

FARNESYL PROTEIN TRANSFERASE INHIBITORS**BACKGROUND**

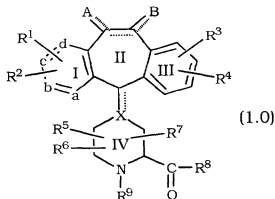
WO 95/10516, published April 20, 1995, WO96/31478, published October 10, 1996, and copending Application Serial No. 09/094687 filed June 15, 1998 discloses tricyclic compounds useful for inhibiting farnesyl protein transferase.

In view of the current interest in inhibitors of farnesyl protein transferase, a welcome contribution to the art would be compounds useful for the inhibition of farnesyl protein transferase. Such a contribution is provided by this invention.

SUMMARY OF THE INVENTION

This invention provides compounds useful for the inhibition of farnesyl protein transferase (FPT). The compounds of this invention are represented by the formula:

A compound of the formula:



or a pharmaceutically acceptable salt or solvate thereof, wherein:
 one of a, b, c and d represents N or N'O', and the remaining a, b, c and d groups represent CR¹ or CR²; or
 each of a, b, c, and d are independently selected from CR¹ or CR²;

each R¹ and each R² is independently selected from H, halo, -CF₃, -OR¹⁰ (e.g., -OCH₃), -COR¹⁰, -SR¹⁰ (e.g., -SCH₃ and -SCH₂C₆H₅), -S(O)_tR¹¹ (wherein t is 0, 1 or 2, e.g., -SOCH₃ and -SO₂CH₃), -N(R¹⁰)₂, -NO₂, -OC(O)R¹⁰, -CO₂R¹⁰, -OCO₂R¹¹, -CN, 5 -NR¹⁰COOR¹¹, -SR¹¹C(O)OR¹¹ (e.g., -SCH₂CO₂CH₃), -SR¹¹N(R⁷⁵)₂ (provided that R¹¹ in -SR¹¹N(R⁷⁵)₂ is not -CH₂-) wherein each R⁷⁵ is independently selected from H or -C(O)OR¹¹ (e.g., -S(CH₂)₂NHC(O)O-t-butyl and -S(CH₂)₂NH₂), benzotriazol-1-yloxy, tetrazol-5-ylthio, or substituted tetrazol-5-ylthio (e.g., alkyl 10 substituted tetrazol-5-ylthio such as 1-methyl-tetrazol-5-ylthio), alkynyl, alkenyl or alkyl, said alkyl or alkenyl group optionally being substituted with halo, -OR¹⁰ or -CO₂R¹⁰;

R³ and R⁴ are the same or different and each independently represents H, any of the substituents of R¹ and R², or R³ and R⁴ 15 taken together represent a saturated or unsaturated C₅-C₇ fused ring to the benzene ring (Ring III);

R⁵, R⁶, and R⁷ each independently represents H, -CF₃, -COR¹⁰, alkyl or aryl, said alkyl or aryl optionally being substituted with -OR¹⁰, -SR¹⁰, -S(O)_tR¹¹, -NR¹⁰COOR¹¹, -N(R¹⁰)₂, -NO₂, 20 -COR¹⁰, -OCOR¹⁰, -OCO₂R¹¹, -CO₂R¹⁰, OPO₃R¹⁰, or R⁵ is combined with R⁶ to represent =O or =S; provided that for the groups -OR¹⁰, -SR¹⁰, and -N(R¹⁰)₂ R¹⁰ is not H;

R¹⁰ represents H, alkyl, aryl, or aralkyl (e.g., benzyl);

R¹¹ represents alkyl or aryl;

25 X represents N, CH or C, and when X is C the optional bond (represented by the dotted line) to carbon atom 11 is present, and when X is CH the optional bond (represented by the dotted line) to carbon atom 11 is absent;

30 the dotted line between carbon atoms 5 and 6 represents an optional bond, such that when a double bond is present, A and B independently represent -R¹⁰, halo, -OR¹¹, -OCO₂R¹¹ or

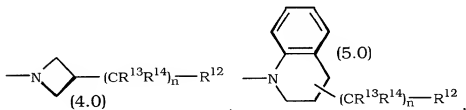
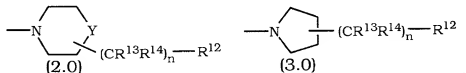
-OC(O)R¹⁰, and when no double bond is present between carbon atoms 5 and 6, A and B each independently represent H₂.

-(OR¹¹)₂, H and halo, dihalo, alkyl and H, (alkyl)₂, -H and

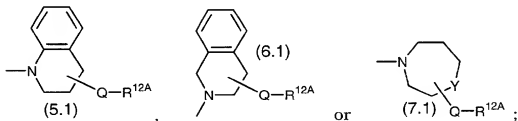
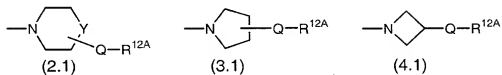
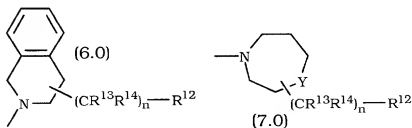
-OC(O)R¹⁰, H and -OR¹⁰, =O, aryl and H, =NOR¹⁰ or -O-(CH₂)_p-O-

5 wherein p is 2, 3 or 4;

R⁹ represents a heterocyclic ring selected from:



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said heterocyclic rings (2.0 to 7.0 and 2.1 to 7.1) being optionally substituted with one or more substituents independently selected from:

- (a) alkyl (e.g., methyl, ethyl, isopropyl, and the like),
 (b) substituted alkyl wherein said substituents are
 selected from: halo, aryl, $-OR^{15}$ or $-N(R^{15})_2$, heteroaryl,
 heterocycloalkyl, cycloalkyl, wherein each R^{15} group is the same or
 5 different, provided that said optional substituent is not bound to a
 carbon atom that is adjacent to an oxygen or nitrogen atom, and
 wherein R^{15} is selected from : H, alkyl, aryl, arylalkyl, heteroaryl,
 heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;
 (c) hydroxyl, with the proviso that carbon atoms
 10 adjacent to the nitrogen, sulfur or oxygen atoms of the ring are not
 substituted with hydroxyl;
 (d) alkyloxy or
 (e) arylalkyloxy;

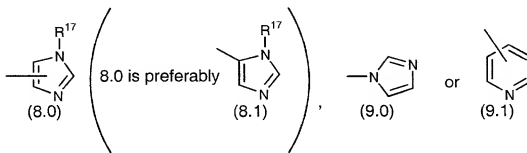
(i.e., each substitutable H atom on each substitutable carbon atom
 15 in said heterocyclic rings is optionally replaced with substituents
 selected from (a) to (e) defined above);

Y represents CH_2 , NR^{16} , O, S, SO , or SO_2 wherein R^{16} is
 selected from: H, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl,
 heteroaryl, heteroarylalkyl, acyl, aroyl, carbamoyl, carboxamido,
 20 alkylsulfonyl, arylsulfonyl, arylalkylsulfonyl, sulfonamido,
 alkylsulfonamido, arylsulfonamido and arylalkylsulfonamido;

n is 0 to 6 (preferably 1-3);

Q represents O or N, provided that Q is not adjacent to a
 heteroatom in the heterocycloalkyl rings of 2.1, 3.1, 4.1, 5.1, 6.1
 25 and 7.1;

R^{12} is selected from:



(e.g., R^{12} is 9.0);

wherein R¹⁷ is selected from: (1) H, (2) alkyl, (3) aryl, (4) arylalkyl, (5) substituted arylalkyl wherein the substituents are selected from halo (e.g., F and Cl) or CN, (6) -C(aryl)₃ (e.g., -C(phenyl)₃, i.e., trityl), (7) cycloalkyl, (8) substituted alkyl (as defined above in (b)), or (9) cycloalkylalkyl;

R^{12a} is selected from rings 8.0, 8.1 or 9.1, defined above;

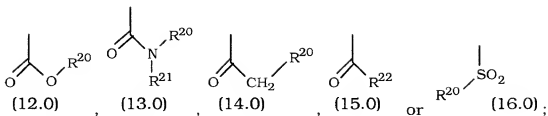
said imidazolyl ring 8.0 and 8.1 optionally being substituted with one or two substituents, said imidazole ring 9.0 optionally being substituted with 1-3 substituents, and said pyridyl ring 9.1

optionally being substituted with 1-4 substituents, wherein said optional substituents for rings 8.0, 8.1, 9.0 and 9.1 are bound to the carbon atoms of said rings and are independently selected from: -NHC(OR)¹⁵, -C(R¹⁸)₂OR¹⁹, -OR¹⁵, -SR¹⁵, F, Cl, Br, alkyl (e.g., methyl, such as 4-methyl in 9.0), substituted alkyl (as defined above in (b)), aryl, arylalkyl, cycloalkyl, or -N(R¹⁵)₂; R¹⁵ is as defined above; each R¹⁸ is independently selected from H or alkyl (preferably -CH₃), preferably H; R¹⁹ is selected from H or -C(O)NHR²⁰, and R²⁰ is as defined below;

R¹³ and R¹⁴ for each n are independently selected from: H, F, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl or -CON(R¹⁵)₂ (wherein R¹⁵ is as defined above), -OR¹⁵ or -N(R¹⁵)₂ provided that the -OR¹⁵ and -N(R¹⁵)₂ groups are not bound to a carbon atom that is adjacent to a nitrogen atom, and provided that there can be only one -OH group on each carbon; and the substitutable R¹³ and R¹⁴ groups are optionally substituted with one or more (e.g., 1-3) substituents selected from: F, alkyl (e.g., methyl, ethyl, isopropyl, and the like), cycloalkyl, arylalkyl, or heteroarylalkyl (i.e., the R¹³ and/or R¹⁴ groups can be unsubstituted or can be substituted with 1-3 of the substituents described above, except when R¹³ and/or R¹⁴ is H); or

R¹³ and R¹⁴, for each n, together with the carbon atom to which they are bound, form a C₃ to C₆ cycloalkyl ring;

R⁹ is selected from:



R²⁰ is selected from: H, alkyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, or heterocycloalkylalkyl, provided that R²⁰ is not H when R⁹ is group

5 12.0 or 16.0;

when R²⁰ is other than H, then said R²⁰ group is optionally substituted with one or more (e.g., 1-3) substituents selected from: halo, alkyl, aryl, -OC(O)R¹⁵ (e.g., -OC(O)CH₃), -OR¹⁵ or -N(R¹⁵)₂, wherein each R¹⁵ group is the same or different, and wherein R¹⁵ is as defined above, provided that said optional substituent is not bound to a carbon atom that is adjacent to an oxygen or nitrogen atom;

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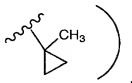
R²¹ is selected from: H, alkyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

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when R²¹ is other than H, then said R²¹ group is optionally substituted with one or more (e.g., 1-3) substituents selected from: alkyl, aryl, wherein each R¹⁵ group is the same or different, and wherein R¹⁵ is as defined above; and

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R²² is selected from cycloalkyl (e.g., cyclopropylmethyl, i.e.,



heterocycloalkyl, aryl (e.g., phenyl), substituted aryl (e.g., halo as a substituent, such as F or Cl), alkyl (e.g., t-butyl), or substituted alkyl or substituted cycloalkyl (substituents include -OH, -CO₂H, and -C(O)NH₂).

25

Thus, in one embodiment of this invention R⁹ is 12.0. In another embodiment R⁹ is 13.0. In another embodiment R⁹ is 14.0.

In another embodiment R⁹ is 15.0. In another embodiment R⁹ is 16.0.

- The compounds of this invention: (i) potentially inhibit farnesyl protein transferase, but not geranylgeranyl protein transferase I, in
5 vitro; (ii) block the phenotypic change induced by a form of transforming Ras which is a farnesyl acceptor but not by a form of transforming Ras engineered to be a geranylgeranyl acceptor; (iii) block intracellular processing of Ras which is a farnesyl acceptor but not of Ras engineered to be a geranylgeranyl acceptor; and (iv)
10 block abnormal cell growth in culture induced by transforming Ras.

- The compounds of this invention inhibit farnesyl protein transferase and the farnesylation of the oncogene protein Ras. Thus, this invention further provides a method of inhibiting farnesyl protein transferase, (e.g., ras farnesyl protein transferase) in
15 mammals, especially humans, by the administration of an effective amount of the tricyclic compounds described above. The administration of the compounds of this invention to patients, to inhibit farnesyl protein transferase, is useful in the treatment of the cancers described below.

- 20 This invention provides a method for inhibiting or treating the abnormal growth of cells, including transformed cells, by administering an effective amount of a compound of this invention. Abnormal growth of cells refers to cell growth independent of normal regulatory mechanisms (e.g., loss of contact inhibition).
25 This includes the abnormal growth of: (1) tumor cells (tumors) expressing an activated Ras oncogene; (2) tumor cells in which the Ras protein is activated as a result of oncogenic mutation in another gene; and (3) benign and malignant cells of other proliferative diseases in which aberrant Ras activation occurs.

- 30 This invention also provides a method for inhibiting or treating tumor growth by administering an effective amount of the tricyclic compounds, described herein, to a mammal (e.g., a human) in need of such treatment. In particular, this invention provides a

method for inhibiting or treating the growth of tumors expressing an activated Ras oncogene by the administration of an effective amount of the above described compounds. Examples of tumors which may be inhibited or treated include, but are not limited to, lung cancer
5 (e.g., lung adenocarcinoma), pancreatic cancers (e.g., pancreatic carcinoma such as, for example, exocrine pancreatic carcinoma), colon cancers (e.g., colorectal carcinomas, such as, for example, colon adenocarcinoma and colon adenoma), myeloid leukemias (for example, acute myelogenous leukemia (AML)), thyroid follicular
10 cancer, myelodysplastic syndrome (MDS), bladder carcinoma, epidermal carcinoma, melanoma, breast cancer and prostate cancer.

It is believed that this invention also provides a method for inhibiting or treating proliferative diseases, both benign and
15 malignant, wherein Ras proteins are aberrantly activated as a result of oncogenic mutation in other genes--i.e., the Ras gene itself is not activated by mutation to an oncogenic form--with said inhibition or treatment being accomplished by the administration of an effective amount of the tricyclic compounds described herein, to a mammal
20 (e.g., a human) in need of such treatment. For example, the benign proliferative disorder neurofibromatosis, or tumors in which Ras is activated due to mutation or overexpression of tyrosine kinase oncogenes (e.g., neu, src, abl, lck, and fyn), may be inhibited or treated by the tricyclic compounds described herein.

25 The tricyclic compounds useful in the methods of this invention inhibit or treat the abnormal growth of cells. Without wishing to be bound by theory, it is believed that these compounds may function through the inhibition of G-protein function, such as ras p21, by blocking G-protein isoprenylation, thus making them
30 useful in the treatment of proliferative diseases such as tumor growth and cancer. Without wishing to be bound by theory, it is believed that these compounds inhibit ras farnesyl protein

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transferase, and thus show antiproliferative activity against ras transformed cells.

DETAILED DESCRIPTION OF THE INVENTION

5 As used herein, the following terms are used as defined below unless otherwise indicated:

MH⁺-represents the molecular ion plus hydrogen of the molecule in the mass spectrum;

BOC-represents tert-butyloxycarbonyl;

10 BOC-ON-represents 1-(tert-butoxycarbonyl)-2-tert-butyl-3-methyl-4-imidazolidinone nitrile;

CBZ-represents -C(O)OCH₂C₆H₅ (i.e., benzyloxycarbonyl);

CBZ-OSUC-represents benzyloxycarbonyl-O-succinimide;

CH₂Cl₂-represents dichloromethane;

15 CIMS-represents chemical ionization mass spectrum;

DEAD-represents diethylazodicarboxylate;

DEC-represents EDC which represents 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide hydrochloride;

DMF-represents N,N-dimethylformamide;

20 Et-represents ethyl;

EtOAc-represents ethyl acetate;

EtOH-represents ethanol;

HOBT-represents 1-hydroxybenzotriazole hydrate;

IPA-represents isopropanol;

25 iPrOH-represents isopropanol;

LAH-represents lithium aluminum hydride;

LDA-represents lithium diisopropylamide;

MCPBA-represents meta-chloroperbenzoic acid;

Me-represents methyl;

30 MeOH-represents methanol;

MS-represents mass spectroscopy;

NMM-represents N-methylmorpholine;

Ph-represents phenyl;

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Pr-represents propyl;

TBDMS-represents tert-butyldimethylsilyl;

TEA-represents triethylamine;

TFA-represents trifluoroacetic acid;

5 THF-represents tetrahydrofuran;

Tr-represents trityl;

alkyl-represents straight and branched carbon chains and
contains from one to twenty carbon atoms, preferably one to six
carbon atoms said cycloalkyl ring being optionally substituted with
10 one or more (e.g., 1, 2 or 3) alkyl groups (e.g., methyl or ethyl) and
when there is more than one alkyl group each alkyl group can be
the same or different;

acyl-represents a G-C(O)- group wherein G represents
alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, -O-alkyl, -O-aryl,
15 or NR²⁵R²⁶ wherein R²⁵ and R²⁶ are independently selected from
alkyl or aryl;

arylalkyl-represents an alkyl group, as defined above,
substituted with an aryl group, as defined below, such that the
bond from another substituent is to the alkyl moiety;

20 aryl-(including the aryl portion of arylalkyl)-represents a
carbocyclic group containing from 6 to 15 carbon atoms and having
at least one aromatic ring (e.g., aryl is a phenyl ring), with all
available substitutable carbon atoms of the carbocyclic group being
intended as possible points of attachment, said carbocyclic group
25 being optionally substituted (e.g., 1 to 3) with one or more of halo,
alkyl, hydroxy, alkoxy, phenoxy, CF₃, -C(O)N(R¹⁸)₂,
-SO₂R¹⁸, -SO₂N(R¹⁸)₂, amino, alkylamino, dialkylamino, -COOR²³ or -
NO₂, wherein R²³ represents alkyl or aryl;

30 aroyl-represents -C(O)aryl wherein aryl is as defined above
(e.g., -C(O)phenyl);

cycloalkyl-represents saturated carbocyclic rings of from 3
to 20 carbon atoms, preferably 3 to 7 carbon atoms, said cycloalkyl
ring optionally substituted with one or more (e.g., 1, 2 or 3) alkyl

groups (e.g., methyl or ethyl) and when there is more than one alkyl group each alkyl group can be the same or different;

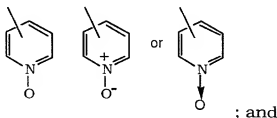
cycloalkylalkyl-represents a cycloalkyl group, as defined above, substituted with an alkyl group, as defined above, such that the bond from another substituent is to the alkyl moiety;

halo-represents fluoro, chloro, bromo and iodo;

heteroalkyl-represents an alkyl group, as defined above, substituted with a heteroaryl group, as defined below, such that the bond from another substituent is to the alkyl moiety;

heteroaryl-represents cyclic groups, optionally substituted with R^3 and R^4 , having at least one heteroatom selected from O, S or N, said heteroatom interrupting a carbocyclic ring structure and having a sufficient number of delocalized pi electrons to provide aromatic character, with the aromatic heterocyclic groups

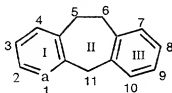
preferably containing from 2 to 14 carbon atoms, e.g., 2- or 3-furyl, 2- or 3-thienyl, 2-, 4- or 5-thiazolyl, 2-, 4- or 5-imidazolyl, 2-, 4- or 5-pyrimidinyl, 2-pyrazinyl, 3- or 4-pyridazinyl, 3-, 5- or 6-[1,2,4-triazinyl], 3- or 5-[1,2,4-thiadiazolyl], 2-, 3-, 4-, 5-, 6- or 7-benzofuranyl, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, triazolyl, 2-, 3- or 4-pyridyl or pyridyl N-oxide (optionally substituted with R^3 and R^4), wherein pyridyl N-oxide can be represented as:



heterocycloalkyl-represents a saturated, branched or unbranched carbocyclic ring containing from 3 to 15 carbon atoms, preferably from 4 to 6 carbon atoms, which carbocyclic ring is interrupted by 1 to 3 hetero groups selected from -O-, -S- or -NR²⁴, wherein R²⁴ represents alkyl, aryl, -C(O)N(R¹⁸)₂ wherein R¹⁸ is as above defined (e.g., -C(O)NH₂) or acyl-(suitable heterocycloalkyl

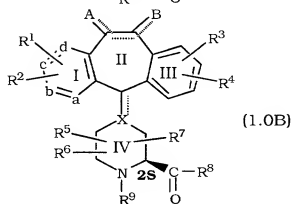
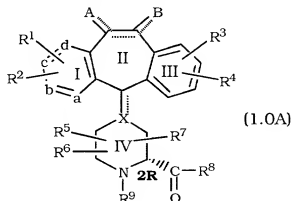
groups include 2- or 3-tetrahydrofuranyl, 2- or 3- tetrahydrothienyl, tetrahydropyranyl, 2-, 3- or 4-piperidinyl, 2- or 3-pyrrolidinyl, 2- or 3-piperazinyl, 2- or 4-dioxanyl, morpholinyl, etc.).

The positions in the tricyclic ring system are:



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The compounds of formula 1.0 include the 2R and 2S isomers shown below (2R is preferred):

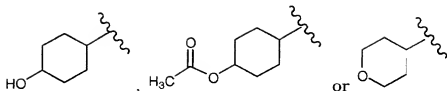


10 Examples of the optional substituents for the R¹² or R^{12A} moiety include: -CH₃, -CH₂OH, -CH₂OC(O)O-cyclohexyl,

-CH₂OC(O)O-cyclopentyl, ethyl, isopropyl, NH₂, and -NHC(O)CF₃.

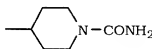
Examples of R¹⁷ include: -C(O)NH-cyclohexyl, -C(phenyl)₃, H, methyl or ethyl.

15 Examples of R²⁰ include t-butyl, i-propyl, neopentyl, cyclohexyl, cyclopropylmethyl,



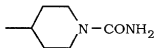
Examples of R^{20} for group 12.0 include: t-butyl, ethyl, benzyl, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-(\text{CH}_2)_2\text{CH}_3$, n-butyl, n-hexyl, n-octyl, p-chlorophenyl, cyclohexyl, cyclopentyl, neopentyl, cyclopropylmethyl

5 or



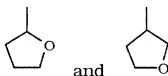
Examples of R^{20} and R^{21} for 13.0 include: cyclohexyl, t-butyl, H, $-\text{CH}(\text{CH}_3)_2$, ethyl, $-(\text{CH}_2)_2\text{CH}_3$, phenyl, benzyl, $-(\text{CH}_2)_2\text{phenyl}$, and $-\text{CH}_3$.

10 Examples of R^{20} for 14.0 include: 4-pyridylNO, $-\text{OCH}_3$, $-\text{CH}(\text{CH}_3)_2$, -t-butyl, H, propyl, cyclohexyl and



Examples for R^{22} for 15.0 include: t-butyl, cyclohexyl, cyclopentyl, cyclobutyl, cyclopropyl, cyclopropylmethyl, phenyl, substituted phenyl (e.g., halo, such as F or Cl),

15



Examples for R^{20} for 16.0 include: methyl, phenyl, isopropyl and cyclohexylmethyl.

Examples of R^{13} and R^{14} include: H, F, phenyl, $-\text{CH}_3$, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-(\text{CH}_2)_3\text{CH}_3$, benzyl, ethyl, p-chlorophenyl, and $-\text{OH}$ (provided that that there can only be one OH on each carbon).

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Cyclopropyl is an Example of the R^{13} and R^{14} group being taken together with the carbon atom to which they are bound to form a cycloalkyl ring.

25

R^1 , R^2 , R^3 , and R^4 are preferably selected from H and halo, and are more preferably selected from H, Br, F and Cl. Representative

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compounds of formula 1.0 include trihalo, dihalo and monohalo substituted compounds, such as, for example: (1) 3,8,10-trihalo; (2) 3,7,8-trihalo; (3) 3,8-dihalo; (4) 8-halo; (5) 10-halo; and (6) 3-halo (i.e., no substituent in Ring III) substituted compounds; wherein
5 each halo is independently selected. Preferred compounds of formula 1.0 include: (1) 3-Br-8-Cl-10-Br-substituted compounds; (2) 3-Br-7-Br-8-Cl-substituted compounds; (3) 3-Br-8-Cl-substituted compounds; (4) 3-Cl-8-Cl-substituted compounds; (5) 3-F-8-Cl-substituted compounds; (6) 8-Cl-substituted compounds;
10 (7) 10-Cl-substituted compounds; (8) 3-Cl-substituted compounds; (9) 3-Br-substituted compounds; and (10) 3-F-substituted compounds.

Substituent a is preferably N or N'O' with N being preferred.

A and B are preferably H₂, i.e., the optional bond is absent
15 and the C5-C6 bridge is unsubstituted.

R⁵, R⁶, and R⁷ are preferably H.

X is preferably N or CH (i.e., the optional bond is absent), and more preferably X is N.

When one or more of the carbon atoms of the imidazole ring
20 8.0 or 9.0 are substituted, the substituents are generally selected from: -N(R¹⁵)₂, -NHC(O)R¹⁵, -C(R¹⁶)₂OR¹⁶, or alkyl, e.g., -CH₃, -CH₂OH, -CH₂OC(O)O-cyclohexyl, -CH₂OC(O)O-cyclopentyl, ethyl, isopropyl, NH₂, or -NHC(O)CF₃.

R¹⁷ is preferably H or alkyl, most preferably H, methyl or
25 ethyl, and more preferably methyl.

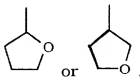
R²⁰ in substituent 12.0 is preferably selected from: alkyl or cycloalkyl, most preferably t-butyl, isopropyl, neopentyl, cyclohexyl or cyclopropylmethyl.

R²⁰ in substituent 13.0 is preferably selected from: alkyl or
30 cycloalkyl; most preferably t-butyl, isopropyl or cyclohexyl. R²¹ is preferably selected from: H or alkyl; most preferably H, methyl or isopropyl; and more preferably H.

R^{20} in substituent 14.0 is preferably selected from: cycloalkyl or alkyl.

R^{22} in substituent 15.0 is preferably selected from: phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, t-butyl,

5 cyclopropylmethyl,



and most preferably selected from: t-butyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

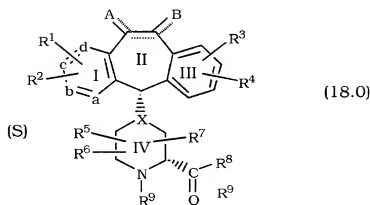
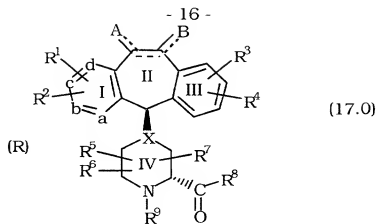
R^{20} in substituent 16.0 is preferably selected from: alkyl or
10 cycloalkylalkyl; most preferably methyl, isopropyl or cyclohexylmethyl; more preferably methyl or isopropyl; and even more preferably methyl.

R^{13} and R^{14} are preferably selected from: H, F, C_1 to C_4 alkyl (e.g., methyl or isopropyl), $-CON(R^{15})_2$ (e.g., $-CONH_2$), $-OR^{15}$ (e.g.,
15 $-OH$), aryl (e.g., phenyl) or arylalkyl (e.g., benzyl); or when R^{13} and R^{14} are taken together to form a cycloalkyl ring, said ring is preferably cyclopropyl cyclopentyl or cyclohexyl. Most preferably R^{13} and R^{14} are H.

For compounds of the invention, n is preferably 1-3, most
20 preferably 1-2.

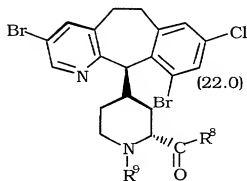
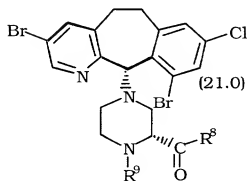
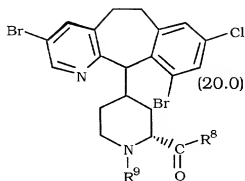
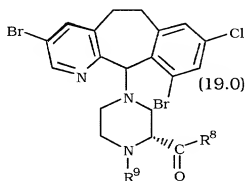
For compounds wherein R^8 is ring 2.0 or 7.0, the $-(CR^{13}R^{14})_n-R^{12}$ substituent can be in the 2-, 3- or 4- position relative to the ring nitrogen, provided that the $-(CR^{13}R^{14})_n-R^{12}$ substituent is not in the 4-position when Y is O, S, SO or SO_2 . Preferably, the -
25 $(CR^{13}R^{14})_n-R^{12}$ substituent is in the 2- or 3- position, and most preferably in the 3- position. More preferably, the $-(CR^{13}R^{14})_n-R^{12}$ substituent is in the 2- position when n is 2, and in the 3- position when n is 1.

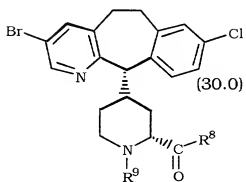
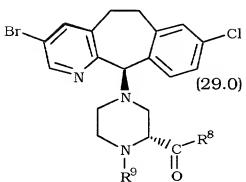
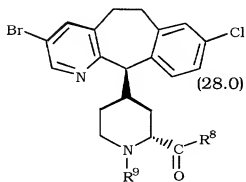
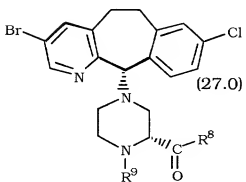
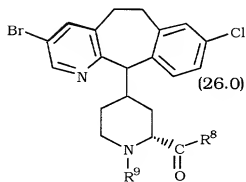
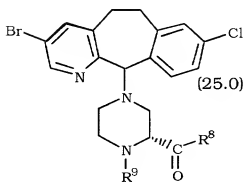
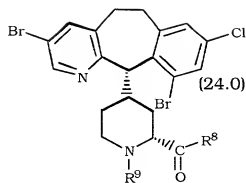
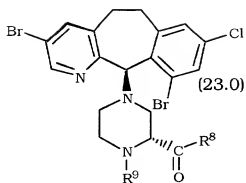
Compounds of formula 1.0, wherein X is N or CH, include,
30 with reference to the C-11 bond, the R- and S- isomers:

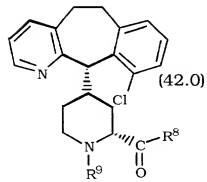
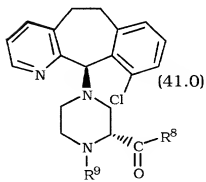
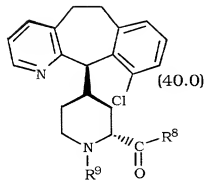
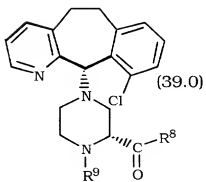
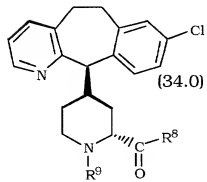
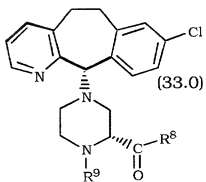
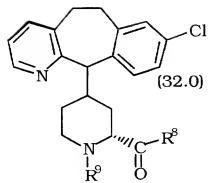
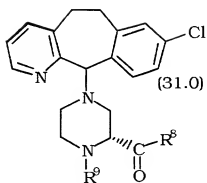


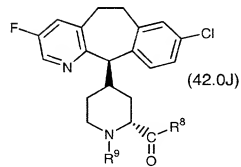
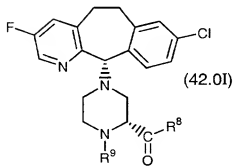
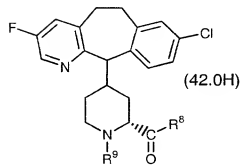
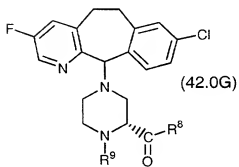
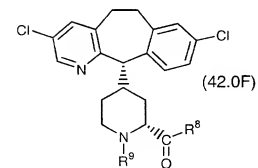
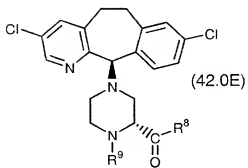
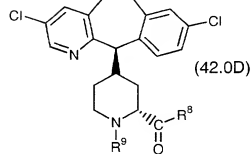
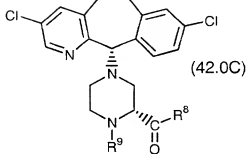
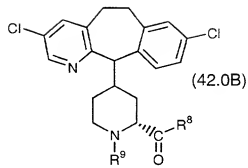
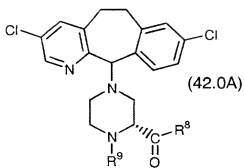
Compounds of this invention include the C-11 R- and S- isomers having the 2S stereochemistry.

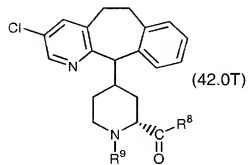
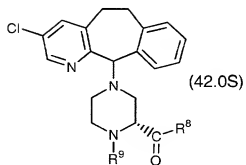
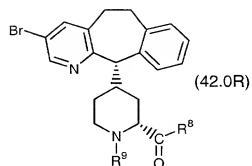
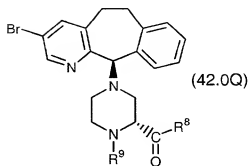
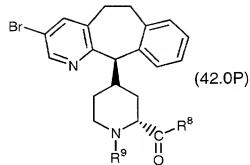
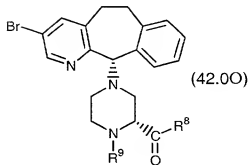
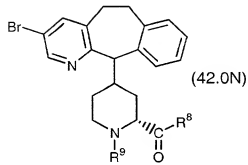
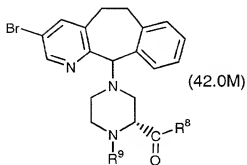
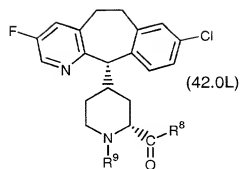
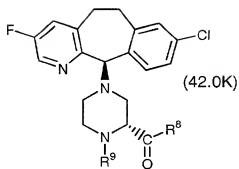
Compounds of this invention include:

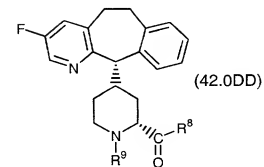
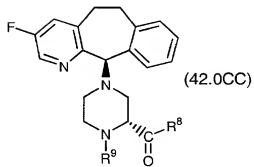
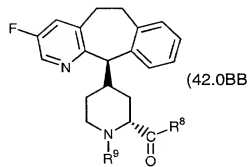
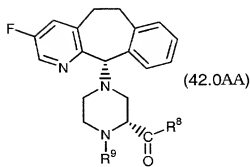
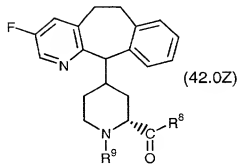
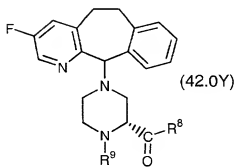
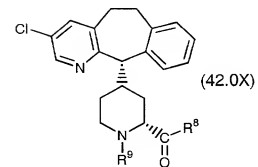
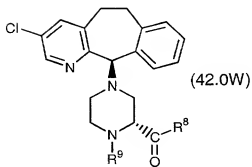
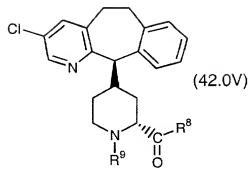
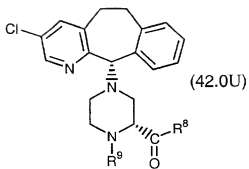










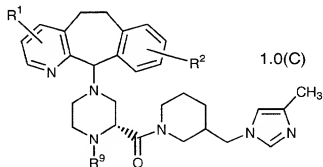


Compounds of the invention also include compounds corresponding to 19.0-42.0 DD, except that Ring I is phenyl instead of pyridyl.

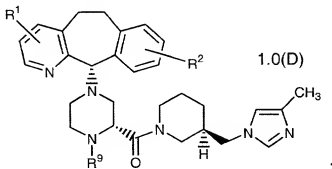
- 5 Compounds of the invention also include compounds corresponding to 19.0-42.0DD, except that Ring I is phenyl instead of Pyridyl, and the compounds have the 2S stereochemistry.

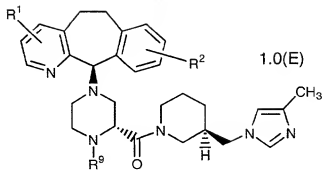
Compounds of this invention also include compounds corresponding to 19.0-42.0DD, except that the compounds have the 2S stereochemistry.

- 10 Compounds of formula 1.0 include compounds of formula 1.0(C)

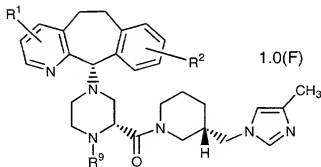


- 15 wherein R¹ is H or halo (preferably Br, Cl or F), and R² is H or halo (preferably Cl), and R⁹ is as defined for formula 1.0. Preferably, R¹ is halo (most preferably Br, Cl or F), and R² is H or halo (preferably Cl). Those skilled in the art will appreciate that compounds of formula 1.0(C) include compounds of formulas 1.0(D) to 1.0(G):



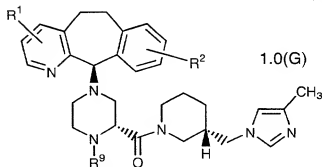


1.0(E)



1.0(F)

; and



1.0(G)

Lines drawn into the ring systems indicate that the indicated bond may be attached to any of the substitutable ring carbon atoms of any ring when more than one ring is present (e.g., ring 5.0).

Certain compounds of the invention may exist in different isomeric (e.g., enantiomers, diastereoisomers, atropisomers) forms. The invention contemplates all such isomers both in pure form and in admixture, including racemic mixtures. Enol forms are also included.

Certain tricyclic compounds will be acidic in nature, e.g. those compounds which possess a carboxyl or phenolic hydroxyl group. These compounds may form pharmaceutically acceptable salts. Examples of such salts may include sodium, potassium, calcium, aluminum, gold and silver salts. Also contemplated are salts formed with pharmaceutically acceptable amines such as

ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine and the like.

Certain basic tricyclic compounds also form pharmaceutically acceptable salts, e.g., acid addition salts. For example, the pyrido-
5 nitrogen atoms may form salts with strong acid, while compounds having basic substituents such as amino groups also form salts with weaker acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic,

10 methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base
15 solution such as dilute aqueous NaOH, potassium carbonate, ammonia and sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and base salts are otherwise equivalent to their respective free base forms for purposes
20 of the invention.

All such acid and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the
25 invention.

The compounds of formula 1.0 can exist in unsolvated as well as solvated forms, including hydrated forms, e.g., hemi-hydrate. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol and the like are equivalent to the
30 unsolvated forms for purposes of the invention.

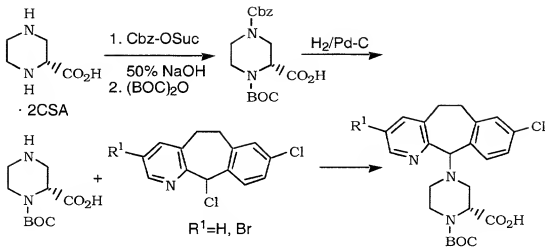
Compounds of the invention may be prepared according to the procedures described in WO 95/10516 published April 20, 1995, WO96/31478 published October 10, 1996, WO 97/23478

- published July 3, 1997, U.S. 5,719,148 issued February 17, 1998,
and copending Application Serial No. 09/094687 filed June 15,
1998 (see also WO98/57960 Published December 23, 1998); the
disclosures of each being incorporated herein by reference thereto;
5 and according to the procedures described below.

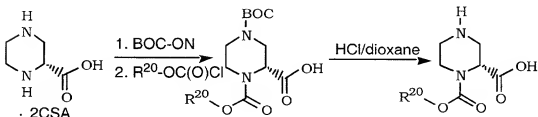
Compounds of the invention can be prepared according to the
reaction schemes described below.

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Scheme 2

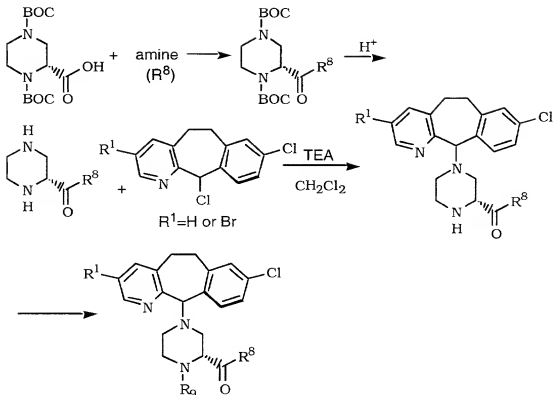


Scheme 3



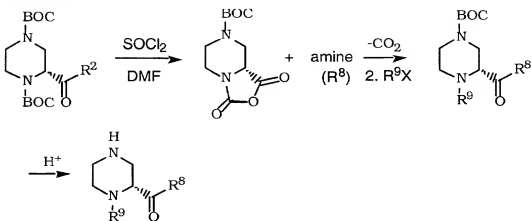
Alternatively, the amine can be coupled to the di-BOC-protected acid intermediate prior to incorporation of the tricycle (Scheme 4). This derivative can be prepared from the di-CSA salt (Scheme 1) upon treatment of the salt with two equivalents (BOC)₂O under basic conditions. Coupling of the desired amine to this intermediate under standard conditions (DEC, HOBT, NMM) gives the amide, which upon TFA-mediated removal of the BOC-protecting groups can be selectively alkylated by the desired tricyclic chloride (TEA, DMF, rt, 48 hours). At this stage, the free amine can be acylated, alkylated, or amidated under conditions obvious to one skilled in the art. When R=Br, chiral HPLC separation can be employed to readily resolve the C-11 diastereomers.

Scheme 4



Finally, the anhydride derivative can be opened with the appropriate amine (rt, CH_2Cl_2), followed by acylation, alkylation, or amidation of the resulting free amine. From there, a similar sequence as illustrated in Scheme 4 (Scheme 5) may be employed for the synthesis of the desired derivatives.

Scheme 5

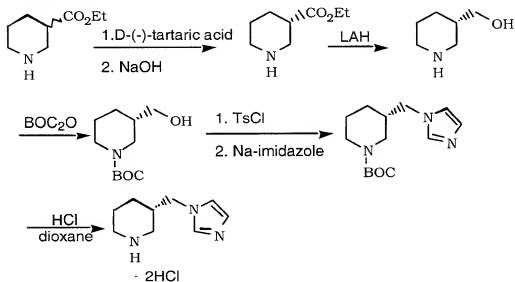


The synthesis of the requisite amines are described generally in the following schemes. In each, one skilled in the art can appreciate the areas where synthetic generalities can be applied for

the synthesis of a wider variety of compounds than those specifically illustrated.

The majority of the 2- and 3-substituted piperidine and pyrrolidine derivatives can be prepared through similar methods as illustrated in Scheme 6 beginning with the appropriate amino alcohol. Likewise, various imidazole derivatives may be prepared by employing the sodium salt of the desired imidazole derivative. This general scheme is not applicable where indicated i.e. piperidines with a 2-hydroxymethyl substituent cannot be prepared using an N-carbamoyl protecting group due to the formation of undesired oxazolones. In these cases the NH must be protected as the N-benzyl or N-allyl derivative.

Scheme 6

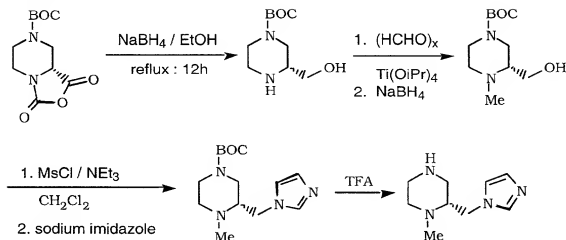


Resolution of ethyl nipecotate with D- or L-tartaric acid (*J. Org. Chem.* (1991) **56**, 1166-1170; *Gazz. Chim. Ital.* (1972) **102**, 189-195.) gives the desired enantiomer which is converted to the free base by treatment with NaOH. Reduction of the acid with LAH followed by protection of the amine as the BOC derivative gives the alcohol. Treatment of the alcohol with p-toluenesulfonyl chloride in pyridine at 0 °C, followed by displacement with the sodium salt of the desired imidazole derivative and removal of the BOC-protecting

group with HCl/dioxane results in the desired amine as the hydrochloride salt.

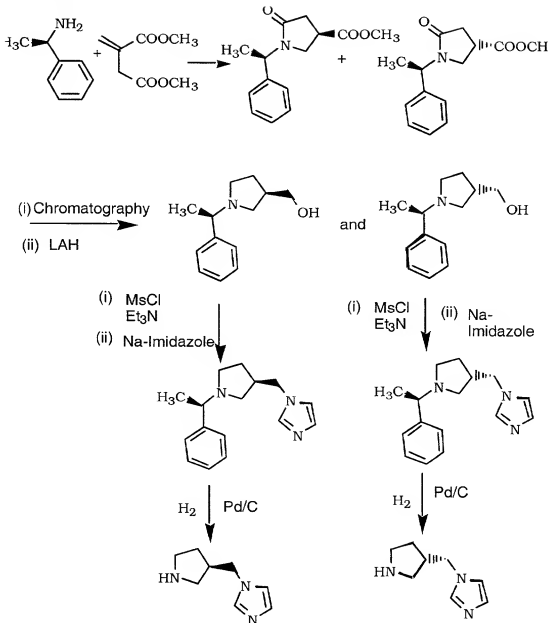
The corresponding 2- and 3-substituted piperazine derivatives can generally be accessed through the anhydride (Scheme 5) as shown in Scheme 7. Ring opening of the anhydride with EtOH followed by reduction with NaBH_4 gives the amino alcohol which can be converted to the N-substituted derivative by reductive amination with paraformaldehyde or another relevant aldehyde. Conversion to the desired imidazole derivative can be accomplished by displacement of the mesylate or tosylate with the sodium salt of the imidazole which upon removal of the BOC-protecting group gives the desired amine.

Scheme 7



The 3-pyrrolidinemethanol intermediates can be synthesized as shown in Scheme 8 (J. Med. Chem. 1990, 71-77). Treatment of the amine with the enoate gives a mixture of diastereomers which are readily separated by silica gel chromatography. Reduction of the amide with LAH and conversion to the imidazole derivative can be carried out as previously described. Catalytic hydrogenation gives the free amine.

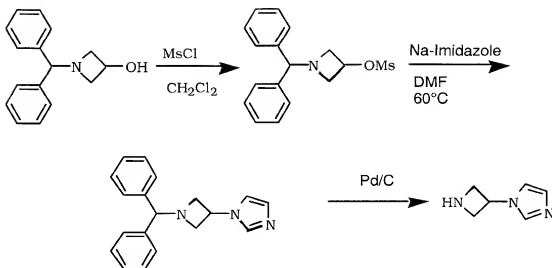
Scheme 8



The 4-membered ring analogs can be synthesized as illustrated in Schemes 9 and 10. When the imidazole is directly

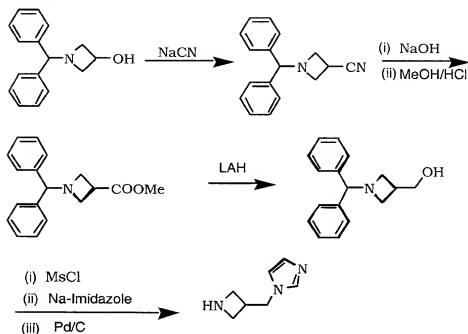
5 attached to the ring, the sequence begins with mesylation of the alcohol followed by displacement with the sodium salt of the desired imidazole derivative. Removal of the benzhydryl protecting group is accomplished by catalytic hydrogenation.

Scheme 9



For 4-membered ring compounds with a methylene spacer between the imidazole and the ring, displacement of the mesylate with NaCN gives the nitrile which is readily hydrolyzed to the acid with NaOH and esterified under Fischer esterification conditions. The desired amine can be realized *via* transformations previously discussed.

10 Scheme 10



The morpholino side chains are prepared beginning with the epichlorohydrin as shown in Scheme 11 (Heterocycle, 38, 1033,

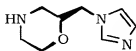
1994). Ring opening of the epoxide with benzyl amine followed by alkylation of the resulting amino alcohol gives the amide. Reduction of the amide with BH_3 gives the morpholine into which the imidazole is incorporated by previously discussed methodology.

- 5 Removal of the N-benzyl protecting group gives the desired amine.

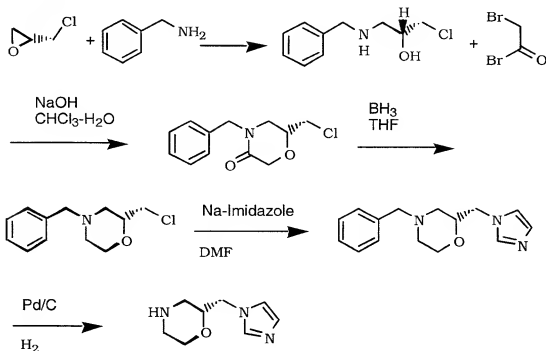
Following the above procedure, but using the epichlorohydrin



gives the amine



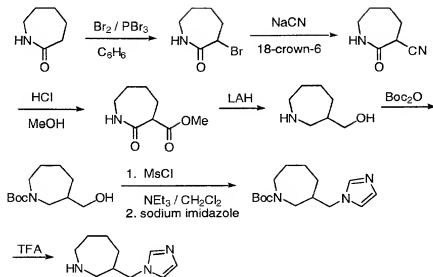
10 Scheme 11



Compounds with a 7-membered ring in the side-chain may be prepared as shown in Scheme 12. α -Bromination of caprolactam followed by displacement with NaCN gives the nitrile. Methanolysis and subsequent reduction with LAH gives the amino alcohol which can easily be converted to the desired compound by previously described methodology.

- 15

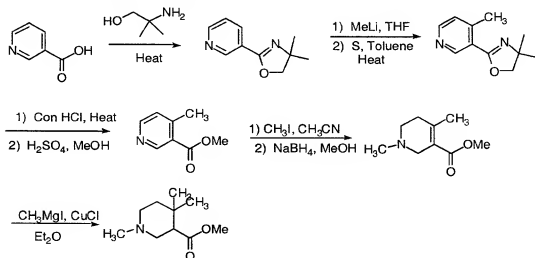
Scheme 12



The 4-substituted piperidine-3-methanol derivatives can be synthesized as illustrated in Scheme 13. Protection of the carboxylic acid as the oxazoline also serves to activate the pyridine ring toward nucleophilic attack by MeLi. Rearomatization with sulfur, hydrolysis of the oxazoline, and esterification gives the ester which upon quaternization and reduction gives the enoate. Conjugate addition with MeI gives the 4,4-dimethyl derivative. This ester may be converted into the desired compound by previously described procedures.

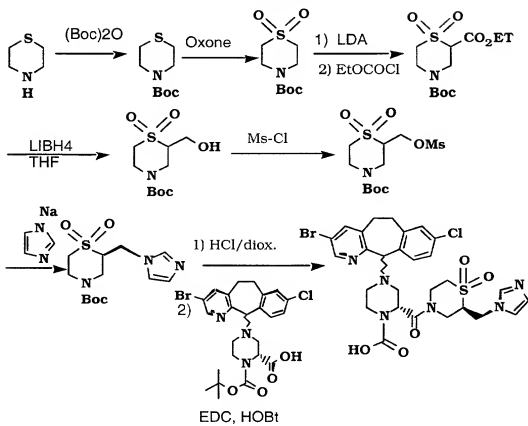
Scheme 13

Ref. *J. Pharm. Sci.* (1992) **81**, 1015; U.S. Pat. (1949) 2546652.

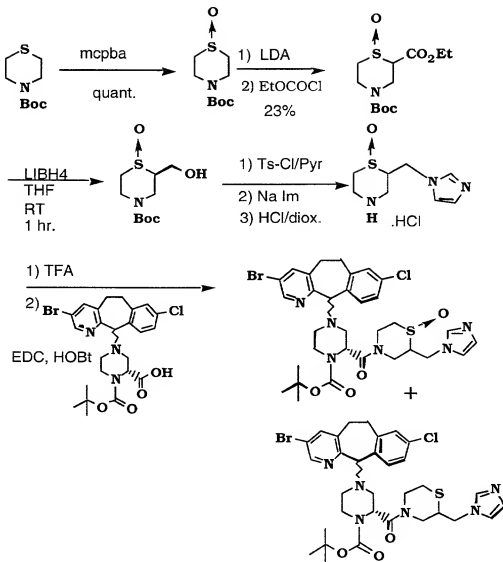


Scheme 14

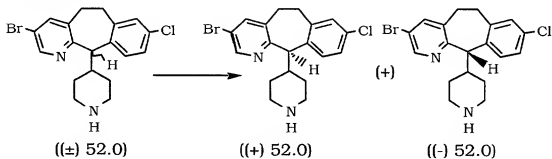
THIOMORPHOLINE DERIVATIVES

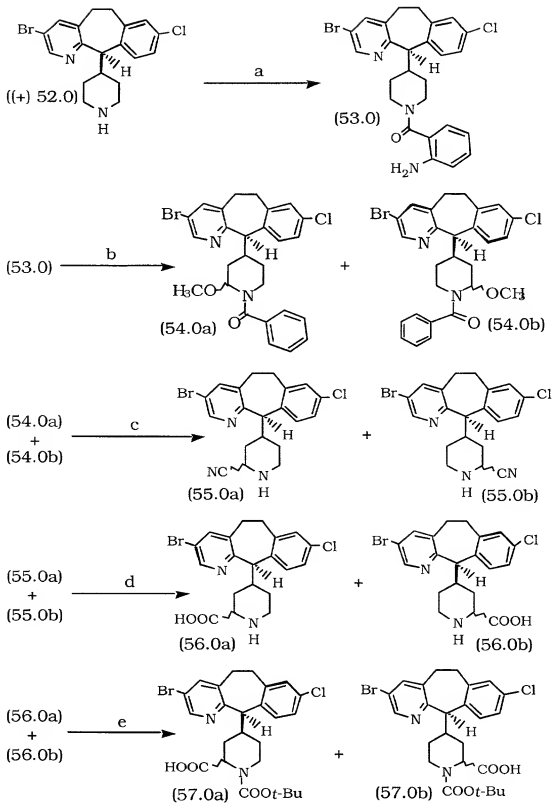


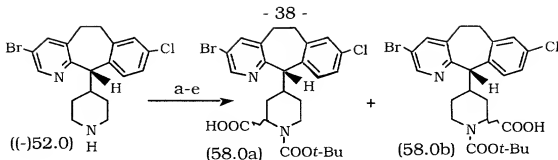
Scheme 15



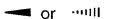
Scheme 16







Those skilled in the art will appreciate that in Scheme 16 the wavy bond to H (\pm 52.0), $-\text{OCH}_3$ (54.0a and 54.0b), $-\text{CN}$ (55.0a and 55.0b), $-\text{COOH}$ (56.0a and 56.0b), $-\text{COOH}$ (57.0a, 57.0b, 58.0a and 58.0b) indicates that the band can be either



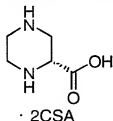
Compound (\pm) 52.0 is resolved following procedures similar to those disclosed in WO97/23478 (published July 3, 1997).

- The reagents used in Reaction Scheme 3 are: Reaction Step a:
- 10 Isatoic anhydride/methylene chloride; Reaction Step b: sodium nitrite/hydrochloric acid/methanol/cuprous chloride; Reaction Step c: (i) aq. hydrochloric acid/methanol/reflux (ii) sodium hydroxide/sodium cyanide; Reaction Step d: conc. hydrochloric acid/reflux.; and Reaction Step e: di-*tert*.butyldicarbonate/-sodium
 - 15 hydroxide/tetrahydrofuran.

Compounds useful in this invention are exemplified by the following preparative examples, which should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous structures within the scope of the invention may be

- 20 apparent to those skilled in the art.

PREPARATIVE EXAMPLE 1

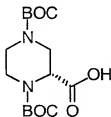


To (R)-(-)-camphorsulfonic acid (2.5 kg) in distilled water

- 25 (1250 mL) at 60 $^{\circ}\text{C}$ was added a solution of the potassium salt of 2-

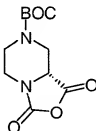
carboxypiperazine (565 gm, 3.35 mol). The mixture was allowed to stir at 95 °C until completely dissolved. The solution was cooled to room temperature and allowed to stand 48 hrs. The resulting precipitate was filtered to obtain a damp solid (1444g). The solids were then dissolved in distilled water (1200 mL) and heated on a steam bath until all solids dissolved. The resulting solution was cooled slowly to room temperature and let stand 72 hrs. The crystalline solids were filtered to give a white crystalline solid (362 g). $[\alpha]_D = -14.9^\circ$.

PREPARATIVE EXAMPLE 2



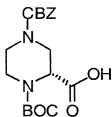
The title compound from Preparative Example 1 (362 gm, 0.608 mol) was dissolved in distilled water (1400 mL) and methanol (1400 mL). 50% NaOH was added to the stirred reaction mixture until the pH reached ~9.5. To this solution was added di-tert.butyl-dicarbonate (336 gm, 1.54 mol) portionwise. The pH of the reaction mixture was maintained at 9.5 with 50% NaOH (total of 175 ml), and the reaction mixture stirred for 2.5 hours to obtain a white precipitate. The reaction mixture was diluted with ice/water (9000 mL) and washed with Et₂O (2000 mL). The Et₂O was discarded and the pH of the aqueous layer adjusted to pH 3.0 by the portionwise addition of solid citric acid and extracted with CH₂Cl₂ (3 X 2000 mL). The organic layers were combined, dried over Na₂SO₄, filtered and evaporated to give the title compound as a white glassy solid (201.6g). FABMS: MH⁺=331.

PREPARATIVE EXAMPLE 3



- To an ice cold solution DMF (49.6 ml) under a nitrogen atmosphere was added, dropwise, SOCl_2 (46.7 ml) over a period of 5 minutes in a 5 L round bottom flask The reaction mixture was allowed to stir for 5 minutes, warmed to room temperature, and stirred 30 minutes. The resulting solution was cooled to 0°C and the title compound from Preparative Example 2 (201.6 gm, 0.61 mmol) in pyridine (51.7 mL) and CH_3CN (1900 mL) was added *via* *canulae*. The resulting solution was warmed to room temperature to obtain a yellowish turbid solution and stirred 18 hours. The reaction mixture was filtered and the filtrate poured into ice water (7L) and then extracted with EtOAc (4 X 2000 mL). The combined organics were dried over Na_2SO_4 , filtered, and evaporated to dryness *in vacuo* to give the title product as a white solid (115.6g, 73% yield).

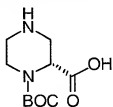
PREPARATIVE EXAMPLE 4



- The title compound from Preparative Example 1 (17.85 gm, 30 mmol) was dissolved in distilled water (180 mL). Dioxane (180 mL) was added and the pH adjusted to ~ 11.0 with 50% NaOH. The reaction mixture was cooled to $0-5^\circ\text{C}$ in an ice-MeOH bath and a solution of benzylchloroformate (4.28 mL, 30 mmol) in dioxane (80 mL) was added over a period of 30-45 minutes while stirring at $0-5^\circ\text{C}$ and keeping the pH at 10.5 to 11.0 with 50% NaOH. After the

addition was complete, stirring was continued for 1 hr. The reaction mixture was then concentrated under reduced pressure. The residue was dissolved in distilled water (180 mL), the pH adjusted slowly to 4.0 with 1N HCl, and extracted with EtOAc (3 X 180 mL). The combined organics were dried over MgSO_4 , filtered, and evaporated to obtain the N,N-di-CBZ-2-carboxy-piperazine byproduct. The pH of the aqueous layer was adjusted to ~10.5 with 50% NaOH and solid $(\text{Boc})_2\text{O}$ (7.86 gm, 36 mmol) was added and the mixture was stirred while keeping the pH at ~10.5 with 50% NaOH. After 1 hr. the pH stabilized. The reaction was checked by tlc (30% MeOH/ NH_3 / CH_2Cl_2) and if not complete, more $(\text{Boc})_2\text{O}$ was added keeping the pH at ~10.5. When reaction was shown to be complete by TLC, the reaction mixture was washed with Et_2O (2 X 180 mL) (check that the product is not in the Et_2O layer and dispose of the Et_2O layer). The aqueous layer was cooled in an ice bath and pH adjusted to 2.0 with 1N HCl (slowly) (get bubbling initially). The aqueous layer was extracted with EtOAc (3 X 200 mL) and the combined organics dried over MgSO_4 , filtered and evaporated *in vacuo* to obtain a white solid (9.68 g, 88% yield).

PREPARATIVE EXAMPLE 5



The title compound from Preparative Example 4 (9.6 gm, 26.3 mmol) was dissolved in absolute EtOH (100 mL) in a hydrogenation vessel. The vessel was flushed with N_2 and 10% Pd/C (3.0g, 50% by weight with water) was added. The mixture was hydrogenated at 55 psi of H_2 for 18 hours during which time a precipitate formed. When the reaction was complete (TLC, 30% MeOH/ NH_3 / CH_2Cl_2), the reaction mixture was filtered through a pad of celite, and the pad washed with EtOH followed by distilled H_2O . The filtrate was

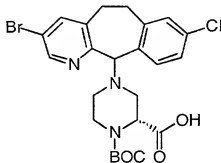
evaporated to ~1/3 the volume and distilled H₂O (200 mL) was added. The resulting solution was extracted with EtOAc (contains pure N,N-Di-Boc-2-carboxy-piperazine which was saved). The water layer was evaporated to dryness with azeotropic removal of residual

- 5 H₂O with methanol (2X) to give pure product (3.98g).

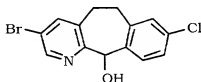
PREPARATIVE EXAMPLE 6

4-(3-bromo-8-chloro-6,11-dihydro-5H benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-1-[(1,1-dimethylethoxy)carbonyl]-2(R)-

- 10 piperazinecarboxylic acid



The tricyclic alcohol



(5.6 gm, 17.33 mmol) was dissolved in CH₂Cl₂ (56 mL) and SOCl₂

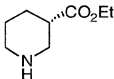
- 15 (2.46 mL) was added while stirring under a dry N₂ atmosphere. After 5 hrs. the tlc was checked (by adding an aliquot of the reaction mixture to 1N NaOH and shaking with CH₂Cl₂ and checking the CH₂Cl₂ layer by tlc using 50% EtOAc/Hexanes as the eluent). The mixture was evaporated to give a gum which was evaporated
- 20 from dry toluene twice and once from CH₂Cl₂ to give a foamy solid. The resulting chloro-tricyclic compound was dissolved in dry DMF (100 mL) and the title compound from Preparative Example 5 (3.98 gm) was added followed by triethylamine (12.11 mL) and the mixture stirred at ambient temperature under a nitrogen
- 25 atmosphere. After 24 hours, the reaction mixture was concentrated and the residue dissolved in EtOAc (200 mL) and

washed with brine. The brine layer was extracted with EtOAc (2X) and the combined organics were dried over MgSO_4 , filtered, and evaporated to give a foamy solid. The solid was chromatographed on a 1 1/2" X 14" column of silica gel eluting with 2L of 0.4% 7N MeOH/ NH_3 : CH_2Cl_2 , 6L of 0.5% 7N MeOH/ NH_3 : CH_2Cl_2 , 2L of 0.65% 7N MeOH/ NH_3 : CH_2Cl_2 , 2L of 0.8% 7N MeOH/ NH_3 : CH_2Cl_2 , 4L of 1% 7N MeOH/ NH_3 : CH_2Cl_2 , 2L of 3% 2N MeOH/ NH_3 : CH_2Cl_2 , 2L of 5% 2N MeOH/ NH_3 : CH_2Cl_2 , 2L of 10% 2N MeOH/ NH_3 : CH_2Cl_2 , 2L of 15% 2N MeOH/ NH_3 : CH_2Cl_2 , 4L of 20% 2N MeOH/ NH_3 : CH_2Cl_2 to obtain 4.63 gm of final product.

PREPARATIVE EXAMPLE 7

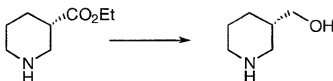
Step A

Ref: *Gazz. Chim. Ital.* (1972) **102**, 189-195; *J. Org. Chem.* (1991) **56**, 1166-1170.



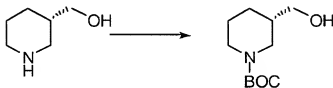
Ethyl nipecotate (70.16g, 0.446 mmol) and D-tartaric acid (67g, 1.0 eq) were dissolved in hot 95% EtOH (350 mL). The resulting solution was cooled to room temperature and filtered and the crystals washed with ice-cold 95% EtOH. The crystals were then recrystallized from 95% EtOH (550 mL) to give the tartrate salt (38.5g, 56% yield). The salt (38.5g) was dissolved in water (300 mL) and cooled to 0 °C before neutralizing with 3M NaOH. The solution was extracted with CH_2Cl_2 (5 X 100 mL) and the combined organics dried over Na_2SO_4 and concentrated under reduced pressure to give a clear oil (19.0g, 89% yield). CIMS: $\text{MH}^+ = 158$.

Step B



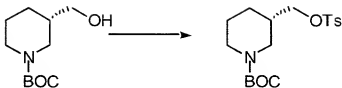
- LAH (118 mL, 1.0 M in Et₂O, 1.0 eq.) was added to a solution of the title compound from Step A (18.5g, 0.125 mmol) in THF (250 mL) at 0 °C over 20 minutes. The resulting solution was warmed slowly to room temperature and then heated at reflux 2 hours. The reaction was cooled to room temperature and quenched by the slow addition of saturated Na₂SO₄. The resulting slurry was dried by the addition of Na₂SO₄, filtered through Celite and concentrated to give a colorless oil (13.7g, 98% crude yield). CIMS: MH⁺=116; [α]_D²⁰ = -8.4° (5.0 mg in 2 mL MeOH).

Step C



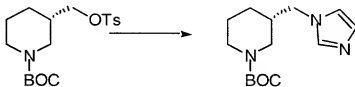
- The title compound from Step B (13.6g, 0.104 mmol) was dissolved in MeOH (100 mL) and H₂O (100 mL) and di-tert-butyl dicarbonate (27.24, 1.2 eq.) was added portionwise keeping the pH >10.5 by the addition of 50% NaOH. The reaction mixture was stirred at room temperature an additional 2.5 hours and concentrated *in vacuo*. The residue was diluted with H₂O (350 mL) and extracted with CH₂Cl₂ (3 X 150 mL). The combined organics were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography using a 50% EtOAc in hexanes solution as eluent to give a white solid (12.13g, 48% yield). FABMS: MH⁺= 216; [α]_D²⁰= +15.2 (5.0 mg in MeOH).

Step D



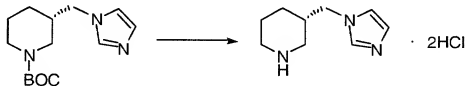
- p-Toluenesulfonyl chloride (12.75g, 1.2 eq.) was added portionwise to the title compound from Step C (12.00g, 55.74 mmol) in pyridine (120 mL) at 0 °C. The resulting solution was stirred 0 °C overnight. The reaction mixture was diluted with EtOAc (300 mL) and washed with cold 1N HCl (5 X 300 mL), saturated NaHCO₃ (2 X 150 mL), H₂O (1 X 100 mL), brine (1 X 100 mL), and dried over Na₂SO₄ and concentrated *in vacuo* to give a pale yellow solid (21.0g, 100% crude yield). FABMS: MH⁺= 370.

Step E



- The title compound from Step D (21.0g, 55.74 mmol) in DMF (300 mL) was treated with sodium imidazole (8.37g, 1.5 eq.) and the resulting solution heated at 60 °C for 2 hours. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was diluted with H₂O (300 mL) and extracted with CH₂Cl₂ (3 X 150 mL). The combined organics were dried over Na₂SO₄, filtered, and concentrated. The crude product was purified by flash chromatography using a 7% MeOH in CH₂Cl₂ solution as eluent to give a pale yellow solid (7.25g, 49% yield). FABMS: MH⁺= 266; [α]_D²⁰= +8.0 (5.0 mg in MeOH).

Step F

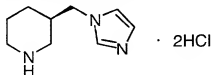


- 46 -

The title compound from Step E (5.50g, 20.73 mmol) stirred at room temperature in 4M HCl in dioxane (50 mL) overnight. The resultant solution was concentrated and the residue triturated with Et₂O to give a yellow solid (4.90g, 99% yield). CIMS: MH⁺ = 166.

5

PREPARATIVE EXAMPLE 8

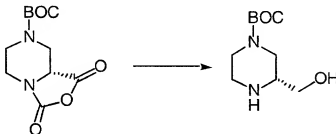


By essentially the same procedure set forth in Preparative Example 7 except using L-tartaric acid instead of D-tartaric acid in Step A, the title compound was prepared.

10

PREPARATIVE EXAMPLE 9

Step A



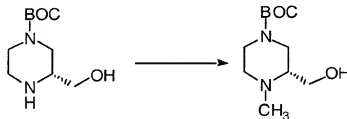
15 A mixture of the piperazine anhydride (2.56 g, 10.00 mmol, 1.0 eq.) and sodium borohydride (965 mg, 25.00 mmol, 2.5 eq.) in absolute ethanol (50 ml) was gently refluxed under a nitrogen atmosphere for 48h. The reaction volume was decreased to approximately 10 ml under house vacuum and diluted with brine

20 (50 ml). The mixture was extracted with ethyl acetate (8 x 25 ml). The combined organic extracts were washed with brine (50 ml), dried over Na₂SO₄, filtered, and concentrated under house vacuum at 30 °C. The residue was flash chromatographed (CH₂Cl₂ : 10% NH₄OH/MeOH = 17:1 v/v) over silica gel to give the title compound

25 (1.09 g, 50%) as a light-yellow, viscous oil. EIMS: m/z 217 ([M+H]⁺, 46%), 161 (B⁺). HR-MS (FAB): Calculated for C₁₀H₂₁N₂O₃ ([M+H]⁺): 217.1552. Found: 217.1549.

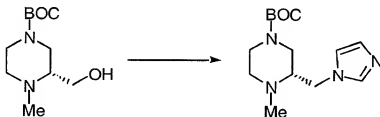
Step B

(Bhattacharyya, S. *Tetrahedron Lett.* **1994**, 35, 2401.)



- A mixture of the title compound from Step A (1.09 g, 5.04 mmol, 1.0 eq.), paraformaldehyde (300 mg, 10.08 mmol, 2.0 eq.), and titanium isopropoxide (1.5 ml, 5.04 mmol, 1.0 eq.) in absolute ethanol (5 ml) was stirred at 70 °C for 30 minutes and at room temperature for another 30 minutes. Sodium borohydride (195 mg, 5.04 mmol, 1.0 eq.) was added to the colorless solution. The solution was stirred at room temperature for 12h and at 60 °C for another 3h. The solution was cooled to 0 °C and treated with a 2.0 M aqueous ammonia solution (25 ml, 50.00 mmol, excess) to give a snow-white suspension. The suspension was filtered through a Celite® 521 plug and the filtrate was extracted with diethyl ether (4 x 25 ml). The ethereal extracts were combined and washed with brine (10 ml), dried over Na₂SO₄, filtered, and concentrated under house vacuum at 30 °C. The residue was flash chromatographed (CH₂Cl₂ : 10% NH₄OH/MeOH = 9:1 v/v) over silica gel to give the title compound (1.10 g, 95%) as a light-yellow, viscous oil. MS (EI): m/z 231 ([M+H]⁺, 59%), 175(B⁺). HR-MS(FAB): Calculated for C₁₁H₂₂N₂O₃ ([M+H]⁺): 231.1709. Found: 231.1716.

Step C

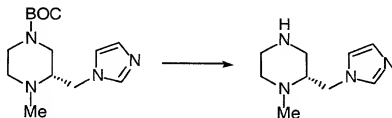


- Methanesulfonyl chloride (296 µl, 3.80 mmol, 1.25 eq.) was added dropwise to a stirred solution of the title compound from Step

B (700 mg, 3.04 mmol, 1.0 eq.) and triethylamine (640 μ l, 4.56 mmol, 1.50 eq.) in anhydrous dichloromethane (5 ml) at 0 °C under a nitrogen atmosphere. The resulting yellow suspension was stirred at 0 °C for 1h and at room temperature for another 3h. The mixture was poured onto brine (25 ml) and extracted with dichloromethane (5 x 10 ml). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated under house vacuum at 25 °C to give a quantitative yield (940 mg) of crude mesylate, which was used directly in the next transformation (*vide infra*) without any attempts at characterization or purification.

A mixture of crude mesylate (940 mg, 3.05 mmol, 1.0 eq.) and sodium imidazole (608 mg, 6.08 mmol, 2.0 eq.) in anhydrous *N,N*-dimethylformamide (10 ml) was stirred at 60 °C for 12h under a nitrogen atmosphere. The brownish mixture was cooled to room temperature and diluted with brine (25 ml). The layers were separated and the aqueous layer was extracted with dichloromethane (4 x 25 ml). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated under house vacuum at 50 °C. The residue was flash chromatographed (CH₂Cl₂ : 10% NH₄OH/MeOH = 19:1 v/v) over silica gel to give the title compound (432 mg, 1.54 mmol, 51%) as a thick, greenish oil. MS (EI): *m/z* 281 ([M+H]⁺, B⁺), 225 (79), 157 (91). HR-MS (FAB): Calculated for C₁₄H₂₅N₄O₂ ([M+H]⁺): 281.1978. Found: 281.1976.

25 Step D



A solution of the title compound from Step C (400 mg, 1.43 mmol, 1.0 eq.) in anhydrous trifluoroacetic acid-dichloromethane (10 ml, 1:1 v/v) was stirred at room temperature under a nitrogen atmosphere for 12h. The volatiles were removed under house

vacuum at 40 °C and the residue was redissolved in 2.0 M aqueous NaOH solution (10 ml). The volatiles were again removed under house vacuum, but at a bath temperature of 60 °C. The residue was flash chromatographed (CH_2Cl_2 : 10% $\text{NH}_4\text{OH}/\text{MeOH}$ = 6:4 v/v) over silica gel to give the title compound (136 mg, 0.76 mmol, 53%) as a thick, yellow oil. MS (EI): m/z 181 ($[\text{M}+\text{H}]^+$, B⁺), 161 (76). HR-MS (FAB): Calculated for $\text{C}_9\text{H}_{17}\text{N}_3$ ($[\text{M}+\text{H}]^+$): 181.1453. Found: 181.1458.

10

PREPARATIVE EXAMPLE 10

Step A

N-Butoxycarbonyl-thiomorpholine

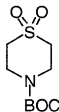


Thiomorpholine (6 gm, 58 mmol) was dissolved in CH_2Cl_2 (200 mL) under a dry nitrogen atmosphere and the reaction mixture cooled in an ice bath. A solution of di-tert.butyl-dicarbonate (15.3 gm, 70 mmol) in CH_2Cl_2 (50 mL) was added dropwise and the reaction mixture stirred for 4 hours. The reaction mixture was washed with brine, followed by saturated NaHCO_3 , dried over MgSO_4 , filtered, and evaporated to obtain 14.37 gm of title product as a crystalline solid. mp= 72.9-78.9 °C.

25

Step B

N-Butoxycarbonyl-thiomorpholinesulfone



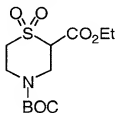
The title compound from Step A (16 gm, 78.7 mmol) was dissolved in 50% $\text{CH}_3\text{OH}-\text{H}_2\text{O}$ (500 mL) at 0°C. A slurry of Oxone[®] (

- 50 -

72.6 gm, 118.05 mmol) was added portionwise while monitoring the pH at 10.5 with 25 % NaOH. After 2 hours, the reaction mixture was filtered and the CH₃OH was evaporated under reduced pressure. The residue was extracted with EtOAc 3 times to obtain
5 15.5 gm (84%) of title product as a crystalline solid. mp= 157-159.2 °C.

Step C

N-Butoxycarbonyl-1-2-carboxyethyl-thiomorpholinesulfone

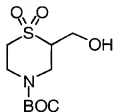


10

The title compound from Step B (3.0 gm, 12.7 mmol) was dissolved in THF (30 mL). The reaction mixture was cooled to -78°C in a dryice acetone bath under a dry nitrogen atmosphere and 8.5 ml of a 1.5 Molar solution of lithium diisopropylamide in
15 cyclohexane (LDA) was added dropwise and the solution stirred for 1/2 hour. Ethylchloroformate (1.83 mL, 19.05 mmol) was added dropwise and the solution stirred at -78 °C for 1 hour. The temperature was allowed to rise to ambient and the reaction mixture stirred an additional 2 hours. The reaction mixture was
20 added to brine and the product extracted three times with EtOAc to obtain 2.87 gm of crude product which was used in the next step without purification.

Step D

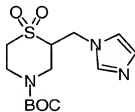
N-Butoxycarbonyl-2-hydroxymethyl-thiomorpholinesulfone



10028251-122001
The crude title compound from Step C was dissolved in 30 ml
5 of THF, cooled in an ice bath, and stirred. A 2M THF solution of
Lithium borohydride (9 mL, 18 mmol) was added dropwise and the
reaction mixture stirred for 3 hours. 1N HCl (~ 10 mL) was added
slowly and the mixture stirred for 5 min. 1N NaOH (~20 mL) was
added and the crude product extracted with ethylacetate, dried over
10 magnesium sulfate, filtered, and evaporated to obtain a crude oil.
The crude oil was chromatographed on silica gel using 20% ethyl
acetate/hexanes to 40% ethylacetate/hexanes to obtain 0.88 gm of
title product as a solid. mp= 126.9-131.9 °C.

15 Step E

N-Butoxycarbonyl-2-imidazolylmethyl-thiomorpholinesulfone



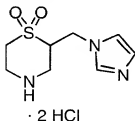
The title compound from Step D (0.56gm, 2.14 mmol) and
20 diisopropylethylamine (0.372 ml, 2.14 mmol) was dissolved in 5 mL
of dichloromethane. Methanesulfonyl chloride (0.198 ml, 2.56
mmol) was added and the reaction mixture stirred under a dry
nitrogen atmosphere for 30 min. The reaction mixture was added
slowly to melted imidazole (2.9 gm, 20 eq.) at 120 °C. After the
25 dichloromethane evaporated the reaction mixture was cooled to
ambient to obtain a brown solid. The solid was dissolved in water
and the product extracted with ethylacetate three times to obtain

- 52 -

0.449 gm of title product. mp= 149.7-151.3 °C, FABMS
(M+1)=316.2.

Step F

- 5 Preparation of 2-imidazolylmethyl-thiomorpholinesulfone



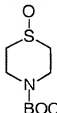
The title compound from Step E (0.44 gm, 1.4 mmol) was dissolved in 5 ml of 4NHCl/dioxane and stirred for 1 hr. The mixture was evaporated to obtain 0.45 gm of title product.

10

PREPARATIVE EXAMPLE 11

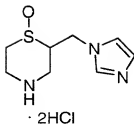
Step A

N-Butoxycarbonyl-thiomorpholinesulfoxide



- 15 N-Butoxycarbonyl-thiomorpholine from Preparative Example
10 Step A (7.07 gm, 58 mmol) was dissolved in 200 ml of
dichloromethane. 50-60% mCPBA (13.7 gm, 80 mmol) was added
portionwise over a period of 15 min. After 2 hours at ambient
temperature the reaction mixture was washed with sat. sodium
20 bisulfite, followed by sat. sodium bicarbonate, and the dried over
magnesium sulfate, filtered, and evaporated to obtain 13.08 gm of a
white solid. FABMS (M+1)=220.

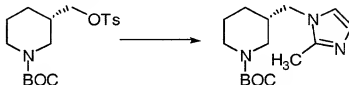
Step B



By essentially the same procedures set forth in Preparative Example 10 Step C-F, the title compound was prepared.

5

PREPARATIVE EXAMPLE 12



2-Methylimidazole (0.27g, 1.3 eq.) was added to a solution of NaH (0.13g, 1.3 eq., 60% in mineral oil) in DMF (5 mL) at room temperature and the resulting solution stirred 20 minutes before adding the title compound from Preparative Example 7 Step D (0.94g, 2.54 mmol). The reaction mixture was heated to 60 °C for 2 hours, cooled to room temperature and concentrated. The crude product was diluted with H₂O (50 mL) and extracted with CH₂Cl₂ (3 X 75 mL). The combined organics were dried over Na₂SO₄, filtered and concentrated in vacuo. The product was purified by flash chromatography using a 7% MeOH in CH₂Cl₂ solution as eluent to give a white solid (0.66g, 93% yield). CIMS: MH⁺ = 280; [α]_D²⁰ = +4.9 (6.5 mg in 2.0 mL MeOH).

20

By essentially the same procedure set forth in Preparative Example 7 Step E, the following title compounds in Column 4 were synthesized beginning with the tosylate in column 2, using the imidazole derivative in Column 3, Table 1:

- 54 -
TABLE 1

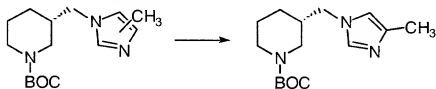
Prep Ex.	Column 2	Column 3	Column 4
13			
14			
			LCMS: MH ⁺ = 280
15			
16			
16(A)			
16(B)			

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TABLE 1 - continued

Prep Ex.	Column 2	Column 3	Column 4
16(C)			
16(D)			
16(E)			

PREPARATIVE EXAMPLE 17



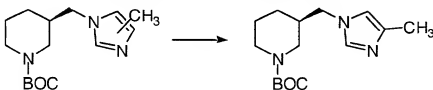
5

To the title compound from Preparative Example 13 (1.0g, 3.58 mmol, 69 : 31 4-Me : 5-Me) in CH_2Cl_2 (10 mL) at 0 °C was added TrCl (0.32g, 1.05 eq. based on 5-Me). The resulting solution was stirred at 0 °C for 2 hours and concentrated under reduced pressure. The crude mixture was purified by flash chromatography

10

using a 50 % acetone in EtOAc solution as eluent to give the title compound as a clear oil (0.50g, 72% yield). CIMS: $MH^+ = 280$.

PREPARATIVE EXAMPLE 18



5

By essentially the same procedure set forth in Preparative Example 17, the title compound was prepared (0.49g, 82% yield).

By essentially the same procedure set forth in Preparative Example 7 Step F except using the compounds prepared in

10 Preparative Examples 12, 13, 14, 15, 16 (Column 2, Table 2), 16A, 16B, 16C, 16D, 17, 18, 71A (step D), 71A (step F) 16E, 72A, 74A, 75A and 76, the amine hydrochlorides in Column 3, Table 2 were prepared:

15

TABLE 2

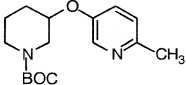
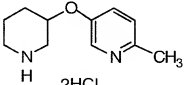
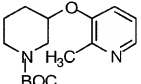
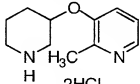
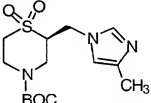
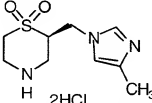
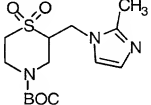
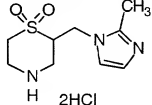
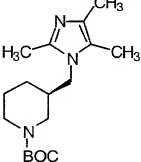
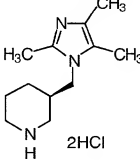
Prep Ex.	N-Boc Amine	Amine
19		 · 2HCl CIMS: $MH^+ = 180$
20		 · 2HCl CIMS: $MH^+ = 180$

TABLE 2 - continued

Prep Ex.	N-Boc Amine	Amine
21		
22		
23		
23(A)		
23(B)		
23(C)		
23(D)		

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TABLE 2 - continued

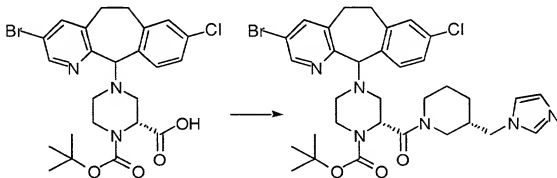
Prep Ex.	N-Boc Amine	Amine
23(E)		 2HCl
23(F)		 2HCl
23(H)		 2HCl
23(I)		 2HCl
23(J)		 2HCl

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TABLE 2 - continued

Prep Ex.	N-Boc Amine	Amine
23(K)		
23(L)		

EXAMPLE 1



The title compound from Preparative Example 6 (1.0g, 1.15 eq.) was added to a solution of the title compound from Preparative Example 1 (2.43g, 3.81 mmol), DEC (0.95g, 1.3 eq.), HOBT (2.57g, 5 eq.) and NMM (2.51 mL, 6.0 eq.) in DMF (50 mL). The resulting solution was stirred at room temperature 24 hours. The reaction mixture was diluted with H₂O until precipitation ceased and the slurry filtered. The precipitate was diluted with CH₂Cl₂ (200 mL), washed with H₂O (2 X 100 mL), dried over Na₂SO₄ and concentrated.

- 60 -

The crude product was purified by flash chromatography using a 5% (10%NH₄OH in MeOH) solution in CH₂Cl₂ as eluent to give a pale yellow solid (1.8g, 68% yield). LCMS: MH⁺= 683.

- 5 By essentially the same procedure set forth in Example 1 only substituting the appropriate amine, one can obtain compounds of the formula shown below with R as listed in Column 2 of Table 3.

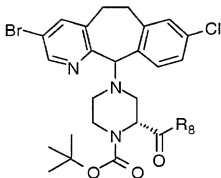


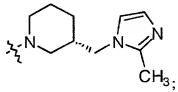
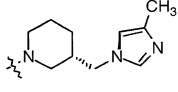
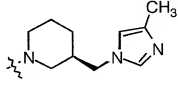
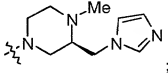
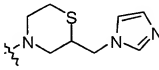
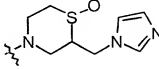
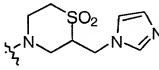
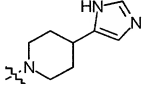
TABLE 3

10

Ex.	R ⁸ =	MP (°C)	CMPD
2	 11-(R,S)	----	LCMS: MH ⁺ = 683
3	 11- (R,S)	126-131	LCMS: MH ⁺ = 697

100221-1528201

TABLE 3 - continued

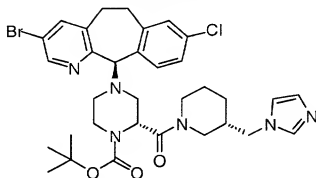
Ex.	R ⁶ =	MP (°C)	CMPD
4	 11- (R,S)	128-133	LCMS: MH ⁺ = 697
4.1		114-121	LCMS: MH ⁺ = 697
4.2		131-135	LCMS: MH ⁺ = 697
5	 11- (R,S)	123-134	FABMS: MH ⁺ = 698
6		---	FABMS: MH ⁺ = 701
7		---	FABMS: MH ⁺ =717
8		179-182	FABMS: MH ⁺ =733
9	 11- (R,S)	175-183	FABMS: MH ⁺ =669

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EXAMPLE 10 and EXAMPLE 11

The title compound from Example 1 was separated into individual (R)- and (S)-isomers by Preparative HPLC with a CHIRALPAK AD column using a 15% iPrOH in hexanes solution
5 with 0.2% DEA as eluent.

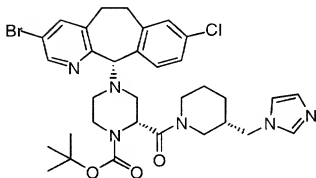
EXAMPLE 10



11-(R)-isomer: retention time (analytical) =8.845 minutes;

10 $[\alpha]_D = +14.0$ (2.72 mg in 2.0 mL MeOH); mp=130-134 °C; LCMS: MH⁺= 683.

EXAMPLE 11



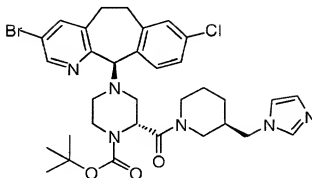
15 11- (S)-isomer: retention time (analytical)=15.416 minutes;

$[\alpha]_D =$; mp=122-127 °C; LCMS: MH⁺= 683.

EXAMPLE 12 and EXAMPLE 13

By essentially the same procedure set forth in Example 10
20 and 11 except using the title compound from Example 2, the title compounds were prepared.

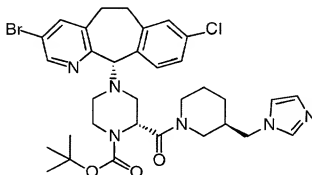
- 63 -
EXAMPLE 12



11- (R)-isomer: retention time (analytical-15% iPrOH: 0.2%
DEA in hexanes)= 18.84 minutes; $[\alpha]_D^{25}$ =; mp=135-138 °C; MS:

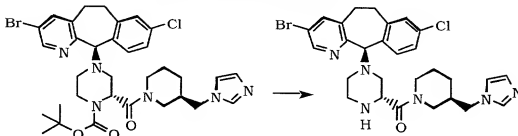
5 MH^+ =683.

EXAMPLE 13



11- (S)-isomer: retention time (analytical-15% iPrOH : 0.2%
10 DEA in hexanes)= 23.758 minutes; $[\alpha]_D^{25}$ =; mp=127-130 °C; MS:
 MH^+ =683.

PREPARATIVE EXAMPLE 24

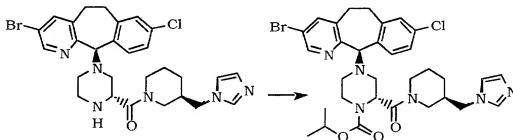


15 The title compound from Example 12 (0.87g, 1.27 mmol) in
 CH_2Cl_2 (9.0 mL) was stirred with TFA (9.0 mL) at room temperature
1 hour. The reaction mixture was cooled to 0 °C and neutralized

with 50% NaOH, separated, and the aqueous layer extracted with CH_2Cl_2 (3 X 200 mL). The combined organics were dried over Na_2SO_4 , filtered, and concentrated *in vacuo* (0.56g, 75% crude yield).

5

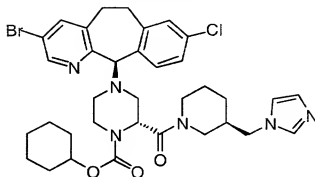
EXAMPLE 14



The title compound from Preparative Example 24 (0.12g, 0.21 mmol) and TEA (0.15 mL, 5.0 eq.) were dissolved in CH_2Cl_2 (5.0 mL) and isopropyl chloroformate (1.05 mL, 5.0 eq.) was added.

- 10 The reaction mixture was stirred at room temperature overnight before adding H_2O (15.0 mL) and extracting with CH_2Cl_2 (2 X 100 mL). The combined organics were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography using a 2.5% (10% NH_4OH in MeOH) solution in CH_2Cl_2 as eluent (0.096g, 69% yield). FABMS: MH^+ = 669; mp = 126-128 °C.

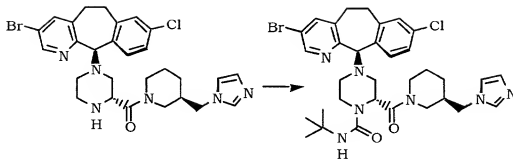
EXAMPLE 15



20

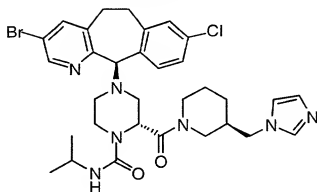
By essentially the same procedure set forth in Example 14 only substituting cyclohexyl chloroformate, the title compound was prepared (0.053g, 44% yield). FABMS: MH^+ = 709; mp = 140-144 °C.

- 65 -
EXAMPLE 16



- The title compound from Preparative Example 24 (0.13g, 0.23 mmol) was dissolved in CH_2Cl_2 (4.0 mL) and t-butylisocyanate (0.13 mL, 5.0 eq.) was added. The resulting solution was stirred at room temperature 2 hours, diluted with H_2O (15 mL) and extracted with CH_2Cl_2 (3 X 50 mL). The combined organics were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography using gradient of 2.5% MeOH in CH_2Cl_2 , 5% MeOH in CH_2Cl_2 , and finally a 10% (10% NH_4OH in MeOH) in CH_2Cl_2 as eluent (0.069g, 44% yield). LCMS: MH^+ = 682; mp = 148-153 °C.

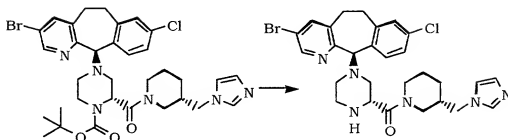
EXAMPLE 17



15

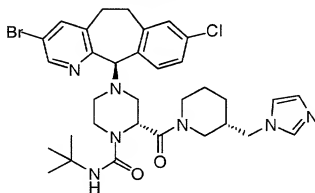
By essentially the same procedure set forth in Example 16 only substituting the isopropylisocyanate, the title compound was prepared (0.09g, 64% yield). LCMS: MH^+ = 668; mp = 132-136 °C.

PREPARATIVE EXAMPLE 25



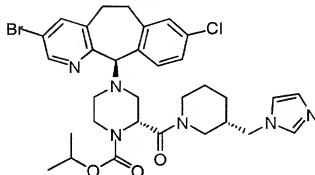
By essentially the same procedure set forth in Preparative Example 24 only using the title compound from Example 10, the title compound was prepared.

EXAMPLE 18



By essentially the same procedure set forth in Example 16 only substituting the title compound from Preparative Example 25, the title compound was prepared. FABMS: $MH^+ = 682$; mp = 112-120 °C.

EXAMPLE 19



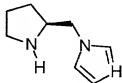
By essentially the same procedure set forth in Example 14 only substituting the title compound from Preparative Example 25,

- 67 -

the title compound was prepared. FABMS: $MH^+ = 669$; mp= 123-132

$^{\circ}C$; $[\alpha]_D^{20} = +16.4^{\circ}$ (4.5 mg in 2.0 mL MeOH)

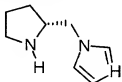
PREPARATIVE EXAMPLE 26



· 2 HCl

- 5 By essentially the same procedure set forth in Preparative Example 7 Steps C to F only beginning with L-prolinol, the title compound was prepared.

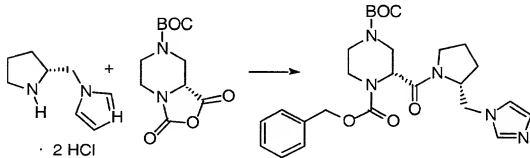
PREPARATIVE EXAMPLE 27



· 2 HCl

- 10 By essentially the same procedure set forth in Preparative Example 24, only beginning with D-prolinol, the title compound was prepared.

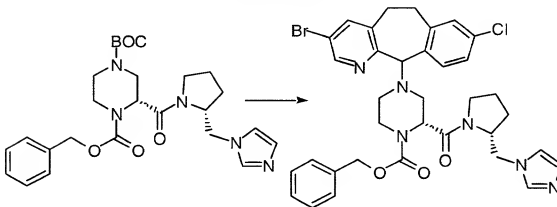
15 PREPARATIVE EXAMPLE 28



- 20 Piperazine anhydride (1.03g, 1.2 eq.) was added portionwise to a solution of the title compound from Preparative Example 27 (0.75g, 3.35 mmol) in CH_2Cl_2 (5.0 mL) and TEA (2.33 mL, 5.0 eq.) and the resulting solution was stirred 10 minutes at room

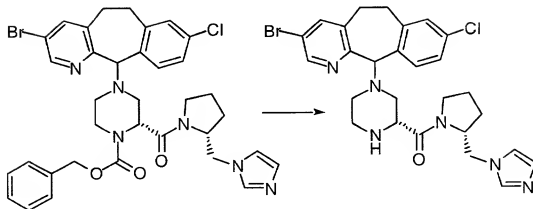
temperature before adding CBZ-OSuc (1.00g, 1.0eq.) The resulting mixture was stirred at room temperature overnight, and concentrated *in vacuo*. The crude product was purified by flash chromatography using a 5% MeOH in CH_2Cl_2 solution as eluent to yield a white solid (0.94g, 56% yield). LCMS: $\text{MH}^+ = 498$; $[\alpha]_D^{20} = +61.6^\circ$ (3.8 mg in 2.0 mL CHCl_3).

EXAMPLE 20



A solution of the title compound from Preparative Example 28 (0.85g, 1.71 mmol) was stirred at room temperature in CH_2Cl_2 (10 mL) and TFA (3 mL) three hours. The reaction mixture was concentrated under reduced pressure and the compound was redissolved in CH_2Cl_2 (7 mL), treated with chloride (Scheme 7 4) (0.29g, 1.0 eq.) and TEA (1.75 mL, 15 eq.). The resulting solution was stirred at room temperature 96 hours. The reaction mixture was diluted with saturated NaHCO_3 (50 mL), water (50 mL), and CH_2Cl_2 (50 mL) and separated. The aqueous layer was extracted with CH_2Cl_2 (2 X 75 mL) and the combined organics dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography using a 6% (10% NH_4OH in MeOH) solution in CH_2Cl_2 as eluent to yield a tan solid (0.29g, 48% yield). mp 80-84 $^\circ\text{C}$; LCMS: $\text{MH}^+ = 703$.

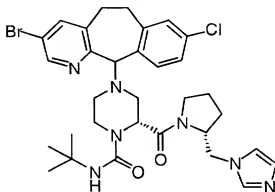
PREPARATIVE EXAMPLE 29



The title compound from Example 20 (0.24g, 0.341 mmol) was stirred at room temperature in HBr/AcOH (2.0 mL) 2 hours.

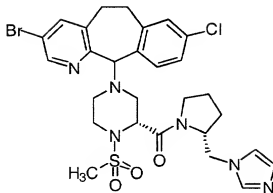
- 5 The reaction mixture was triturated with Et₂O and any remaining AcOH removed by azeotrope with toluene to give the HBr salt which was neutralized with 1N NaOH and extracted into CH₂Cl₂ (3 X 50 mL). The combined organics were dried over Na₂SO₄, filtered, and concentrated *in vacuo* to give a tan solid (0.18g, 95% yield)
- 10 which was used without further purification. LCMS: MH⁺= 569.

EXAMPLE 21



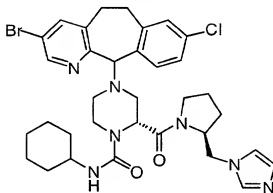
- 15 By essentially the same procedure set forth in Example 16, only using the title compound from Preparative Example 29, the title compound was prepared (0.029g, 50% yield). LCMS: MH⁺= 668; mp=137-139 °C.

- 70 -
EXAMPLE 22



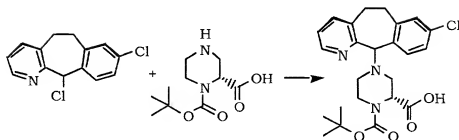
To the title compound from Preparative Example 29 (0.10g, 0.175 mmol) and TEA (0.037 mL, 1.5 eq.) in CH_2Cl_2 (5.0 mL) was added MsCl (0.16 μL , 1.2 eq.) and the resulting solution was stirred at room temperature overnight. The resulting solution was quenched by the addition of saturated NaHCO_3 (10 mL), diluted with H_2O (25 mL) and extracted with CH_2Cl_2 (3 X 25 mL). The combined organics were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography using a 10% (10% NH_4OH in MeOH) solution in CH_2Cl_2 as eluent to yield a tan solid (0.70g, 64% yield). LCMS: $\text{MH}^+ = 647$; mp= 135-141 $^\circ\text{C}$.

EXAMPLE 23

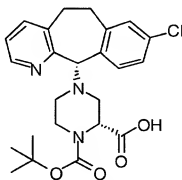


By essentially the same procedure set forth in Example 22 only substituting the amine hydrochloride from Preparative Example 26 and quenching with cyclohexyl isocyanate in place of CBC-OSuc, the title compound was prepared. LCMS: $\text{MH}^+ = 669$; mp=187.

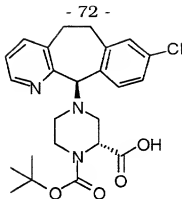
PREPARATIVE EXAMPLE 30



- Tricyclic chloride (5.04g, 1.1 eq.) was added to a solution of
 5 the title compound from Preparative Example 5 (4.0g, 17.3 mmol)
 and TEA (12.05 mL, 5 eq.) in DMF (60 mL). The resulting solution
 was stirred at room temperature 72 hours at which time the
 reaction mixture was concentrated under reduced pressure. The
 residue was diluted with 3M NaOH and extracted with EtOAc. The
 10 aqueous layer was neutralized with 50% citric acid and extracted
 with EtOAc. The combine organics were dried over Na₂SO₄, filtered,
 and concentrated in vacuo. The crude product was purified by
 flash chromatography using a 12% (10% NH₄OH in MeOH) solution
 in CH₂Cl₂ as eluent to give the C-11 (S)-isomer (2.13g, 54%) as the
 15 first eluting isomer and the C-11 (R)-isomer (2.4g, 61%) as the
 second eluting isomer.



11- (S)-isomer (first eluting isomer): $[\alpha]^{20}_D = -13.4^\circ$ (3.72 mg in
 2.0 mL MeOH); LCMS: MH⁺ = 458.



11- (R)-isomer (second eluting isomer): $[\alpha]_D^{20} = +84.9^\circ$ (5.18 mg in 5.0 mL MeOH); FABMS: $MH^+ = 458$.

5

EXAMPLES 24-35G

By essentially the same procedure set forth in Example 1 only using the title compounds from Preparative Example 30 (individual C-11 (S)- and (R)-isomers) as listed in column 2 of Table 4 and substituting the appropriate amine, the title compounds of the

10 formula shown below with R^8 as listed in column 3 of Table 4 are obtained.

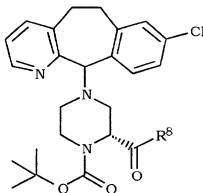
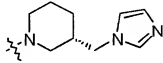
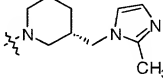
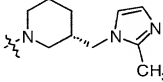
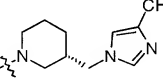
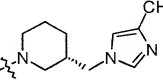
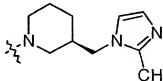


TABLE 4

15

EX.	C-11 isomer	$R^8 =$	MP (°C)	CMPD
24	S		115- 126	LCMS: $MH^+ = 605$

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TABLE 4 - continued

EX.	C-11 isomer	R ⁸ =	MP (°C)	CMPD
25	R		124- 143	LCMS: MH ⁺ = 605
26	S		120- 132	LCMS: MH ⁺ = 619
27	R		110- 119	LCMS: MH ⁺ = 619
28	S		115- 132	LCMS: MH ⁺ = 619
29	R		109- 124	LCMS: MH ⁺ = 619
30	S		105- 119	LCMS: MH ⁺ = 619

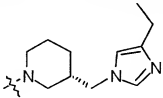
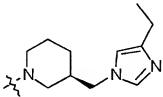
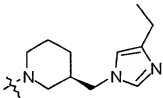
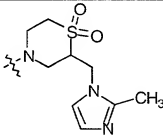
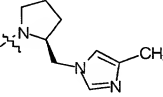
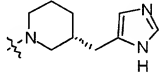
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TABLE 4 - continued

EX.	C-11 isomer	R ⁸ =	MP (°C)	CMPD
31	R		121- 142	LCMS: MH ⁺ = 619
32	S		80-85	LCMS: MH ⁺ = 619
33	R		117- 120	LCMS: MH ⁺ = 619
34	S		----	LCMS: MH ⁺ =634
35	R		----	LCMS: MH ⁺ =634
35(A)	S		110- 112	MS: MH ⁺ =633

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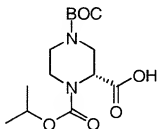
TABLE 4 - continued

EX.	C-11 isomer	R ⁸ =	MP (°C)	CMPD
35(B)	R		89-92	MS: MH ⁺ =633
35(C)	S		104- 106	MS: MH ⁺ =633
35(D)	R		79-81	MS: MH ⁺ =633
35(E)	R		---	FABMS: MH ⁺ =670
35(F)	S		115- 120	LCMS: MH ⁺ =606
35(G)	S		97- 122	LCMS: MH ⁺ =605

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PREPARATIVE EXAMPLE 31

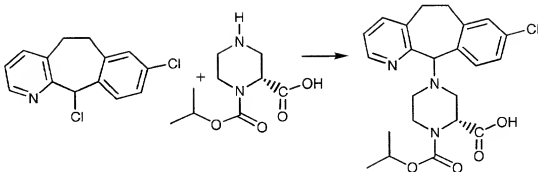
Step A



- 50% NaOH was added to a solution of the title compound
- 5 from Preparative Example 1 (11.47g, 19.28 mmol) in dioxane : H₂O (1:1, 64 mL) until the pH was ~11.5 and BOC-ON (5.22g, 1.1 eq.) was added in two portions. 50% NaOH was added to keep the pH at ~11.5. When the pH stabilized the resulting solution was stirred at room temperature overnight. The pH was adjusted to ~9.5 by the
- 10 addition of 1M HCl and isopropyl chloroformate (21.21 mL, 1.0 M in toluene, 1.1 eq.) was added. The resulting solution was kept at pH ~9.5 and stirred 3 days. The reaction mixture was concentrated and extracted with Et₂O, readjusting the pH to 9.5 following each extraction. When the pH stabilized at ~9.5 for 3 consecutive
- 15 extractions the aqueous layer was acidified to pH ~4.5 with 50% citric acid and to pH~3 with 1M HCl and extracted with EtOAc (3 x 100 mL). The combined organics were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a white solid (5.8g, 90% yield). FABMS: MH⁺ = 317. Treatment of the product with
- 20 TFA yielded the deprotected amine which was used without further purification.

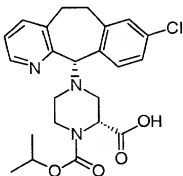
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Step B

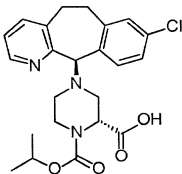


By essentially the same procedure set forth in Preparative Example 30 only substituting the compound from Preparative

- 5 Example 31 Step A, the title compound was prepared and separated into C-11 isomers:



11- (S)-isomer (first eluting isomer): LCMS: $MH^+ = 444$.



10 11- (R)-isomer (second eluting isomer): LCMS: MH^+ =444.

EXAMPLES 36-41I

By essentially the same procedure set forth in Example 1 only substituting the title compounds from Preparative Example 31

- 15 (individual C-11 (S)- and (R)-isomers) and substituting the

appropriate amine, the compounds of the formula shown below with R⁸ as listed in column 3 of Table 5 are obtained.

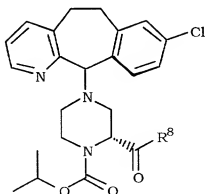
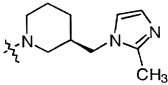
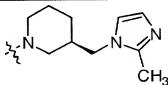
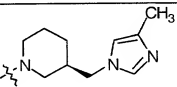
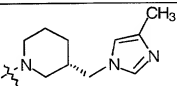
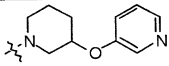
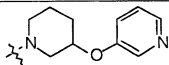


TABLE 5

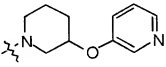
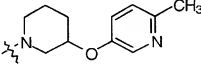
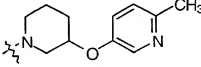
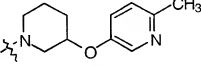
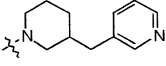
EX.	C-11 isomer	R ⁸ =	MP (°C)	CMPD
36	S		123- 132	LCMS: MH ⁺ =605
37	R		95- 111	LCMS: MH ⁺ =605
38	S		92- 101	FABMS: MH ⁺ =605
39	R		111- 125	FABMS: MH ⁺ =605

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TABLE 5 - continued

EX.	C-11 isomer	R ⁸ =	MP (°C)	CMPD
40	S		107- 112	FABMS: MH ⁺ =605
41	R		95- 100	FABMS: MH ⁺ =605
41(A)	S		117- 120	LCMS: MH ⁺ =605
41(B)	R		101- 120	LCMS: MH ⁺ =605
41(C)	S	 Isomer 1,2	104- 108	LCMS: MH ⁺ =604
41(D)	S	 Isomer 1	98- 100	LCMS: MH ⁺ =604

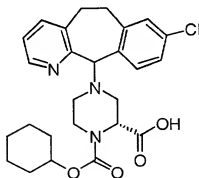
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TABLE 5 - continued

EX.	C-11 isomer	R ⁶ =	MP (°C)	CMPS
41(E)	S	 Isomer 2	100- 103	LCMS: MH ⁺ =604
41(F)	S	 Isomer 1,2	90- 105	LCMS: MH ⁺ =618
41(G)	S	 Isomer 1	90- 105	LCMS: MH ⁺ =618
41(H)	S	 Isomer 2	95- 105	LCMS: MH ⁺ =618
41(I)	S	 Isomer 1,2	95- 104	LCMS: MH ⁺ =602

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PREPARATIVE EXAMPLE 32



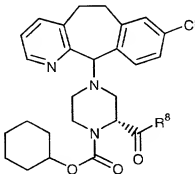
By essentially the same procedure set forth in Preparative Example 31 only substituting cyclohexyl chloroformate for isopropyl chloroformate in Step A, the title compounds (C-11 (S)- and (R)- isomers) were prepared and separated into individual diastereomers:

11-(S)-isomer (first eluting isomer): FABMS: $MH^+=484$.

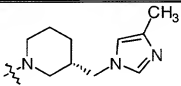
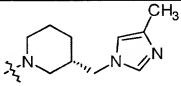
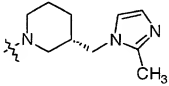
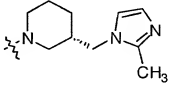
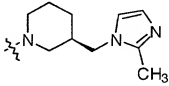
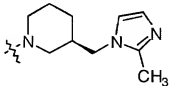
11-(R)-isomer (second eluting isomer): FABMS: $MH^+=484$.

EXAMPLES 42-47CC

By essentially the same procedure set forth in Example 1 only substituting the title compounds from Preparative Example 32 (individual C-11 (S)- and (R)-isomers) and substituting the appropriate amine, the compounds of the formula shown below with R^8 as listed in Column 3 of Table 6 can be obtained.



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TABLE 6

EX.	C-11 isomer	R ³ =	MP (°C)	CMPD
42	S		99- 113	FABMS: MH ⁺ =645
43	R		108- 118	FABMS: MH ⁺ =645
44	S		112- 135	FABMS: MH ⁺ =645
45	R		108- 123	FABMS: MH ⁺ =645
46	S		91- 94	FABMS: MH ⁺ =645
47	R		100- 106	FABMS: MH ⁺ =645

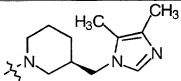
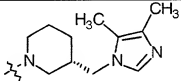
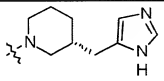
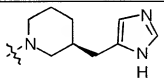
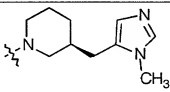
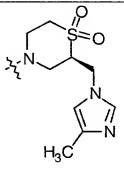
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TABLE 6 - continued

EX.	C-11 isomer	R ⁸ =	MP (°C)	CPMD
47(A)	S		122- 127	FABMS: MH ⁺ =645
47(B)	R		133- 139	FABMS: MH ⁺ =645
47(K)	R		74- 76	MS: MH ⁺ =659
47(D)	S		66- 68	MS: MH ⁺ =659
47(E)	R		85- 89	MS: MH ⁺ =659
47(F)	S		48- 52	MS: MH ⁺ =659

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TABLE 6 - continued

EX.	C-11 isomer	R ⁸ =	MP (°C)	CMPD
47(G)	S		98- 130	LCMS: MH ⁺ =659
47(H)	S		106- 125	LCMS: MH ⁺ =659
47(I)	S		113- 115	LCMS: MH ⁺ =631
47(J)	S		106- 132	LCMS: MH ⁺ =631
47(K)	S		101- 123	LCMS: MH ⁺ =645
47(L)	S		---	FABMS: MH ⁺ =696

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TABLE 6 - continued

EX.	C-11 isomer	R ⁸ =	MP (°C)	CPMPD
47(M)	R		---	FABMS: MH ⁺ =696
47(N)	S		---	FABMS: MH ⁺ =696
47(O)	R		---	FABMS: MH ⁺ =696
47(P)	S		---	FABMS: MH ⁺ =674
47(Q)	R		---	FABMS: MH ⁺ =674

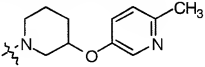
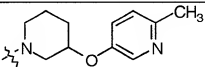
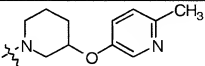
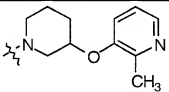
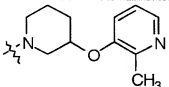
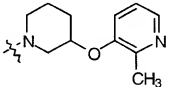
10028251-122001

- 86 -
TABLE 6 - continued

EX.	C-11 isomer	R ⁸ =	MP (°C)	CPMPD
47(R)	S		---	FABMS: MH ⁺ =674
47(S)	S		---	FABMS: MH ⁺ =646
47(T)	S		---	FABMS: MH ⁺ =646
47(U)	S	 Isomer 1	117- 120	FABMS: MH ⁺ =644
47(V)	S	 Isomer 2	105- 108	FABMS: MH ⁺ =644

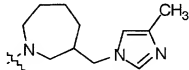
10028251-122001

- 87 -
TABLE 6 - continued

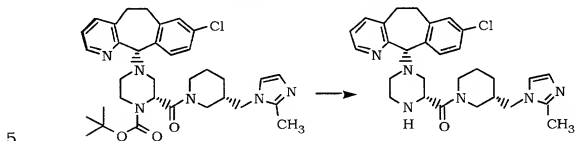
EX.	C-11 isomer	R ⁸ =	MP (°C)	CPMD
47(W)	S	 (Isomer 1,2)	94- 113	LCMS: MH ⁺ =658
47(X)	S	 Isomer 1	94- 113	FABMS: MH ⁺ =658
47(Y)	S	 Isomer 2	100- 118	LCMS: MH ⁺ =658
47(Z)	S	 Isomer 1,2	100- 108	LCMS: MH ⁺ =658
47(AA)	S	 Isomer 1	100- 115	LCMS: MH ⁺ =658
47(BB)	S	 Isomer 2	108- 120	LCMS: MH ⁺ =658

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TABLE 6 - continued

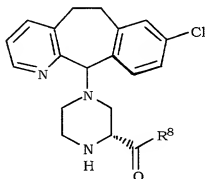
EX.	C-11 isomer	R ⁸ =	MP (°C)	CPD
47(CC)	S	 Isomer 1,2	108- 113	FABMS: MH ⁺ =659

PREPARATIVE EXAMPLE 33

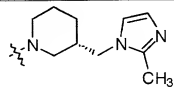
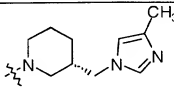
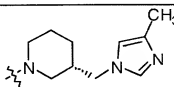
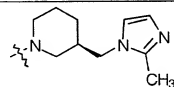
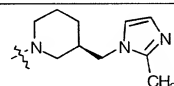
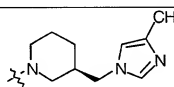


By essentially the same procedure set forth in Preparative Example 24, only using the title compounds from Example 26, the title compound was prepared.

- 10 By essentially the same procedure set forth in Preparative Example 33 only substituting the compound from the example listed in column 2 of Table 7, the title compounds of the formula shown below with R⁸ as in column 4 of Table 7 were prepared:

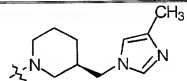


- 89 -
TABLE 7

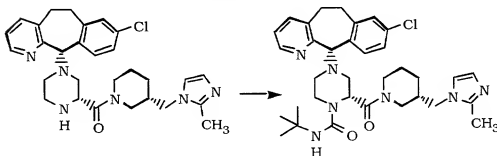
Prep. Ex.	Ex.	C-11 Isomer	R ⁸ =
34	27	R	
35	28	S	
36	29	R	
36(A)	30	S	 MP=99-112°C LCMS: MH ⁺ =618
36(B)	31	R	 MP=110-123°C LCMS: MH ⁺ =618
36(C)	32	S	 MP=96-106°C LCMS: MH ⁺ =618

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TABLE 7 - continued

Prep. Ex.	Ex.	C-11 Isomer	R ⁸ =
36(D)	33	R	 MP=150-152°C LCMS: MH ⁺ =618

EXAMPLE 48

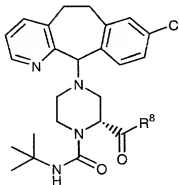


5

By essentially the same procedure set forth in Example 16 only substituting the title compound from Preparative Example 33, the title compound was prepared. FABMS: MH⁺=618; mp= 111-140 °C.

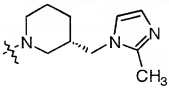
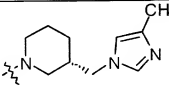
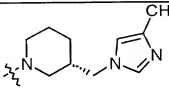
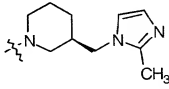
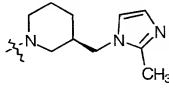
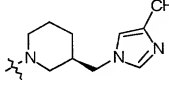
10

By essentially the same procedure set forth in Example 48 only substituting the title compounds from the Preparative Example listed in column 2 of Table 8, the title compounds of the formula shown below with R⁸ listed as in column 4 of Table 8 are obtained.



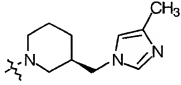
15

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TABLE 8

Ex.	Prep. Ex.	C-11 isomer	R ^a =	MP (°C)	COMPD
49	34	R		102-125	FABMS: MH ⁺ = 618
50	35	S		123-135	FABMS: MH ⁺ = 618
51	36	R		112-130	FABMS: MH ⁺ = 618
51A	36A	S		99-112	LCMS: MH ⁺ = 618
51B	36B	R		110-123	LCMS: MH ⁺ = 618
51C	36C	S		96-106	LCMS: MH ⁺ = 618

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TABLE 8 - continued

Ex.	Prep. Ex.	C-11 isomer	R ⁸ =	MP (°C)	COMPD
51D	36D	R		150-152	LCMS: MH ⁺ =61 8

PREPARATIVE EXAMPLE 48

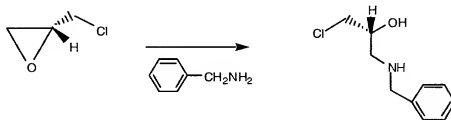
5 (R) AND (S)-[2-(1H-IMIDAZOL-1-YL)METHYL]MORPHOLINES



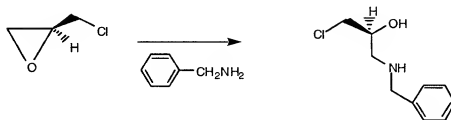
Step A

(R) AND (S)-3-CHLORO-1(BENZYLAMINO)-2-PROPANOLS

(T.Mori et al Heterocycles 38,5 1033, 1994)



(R)



(S)

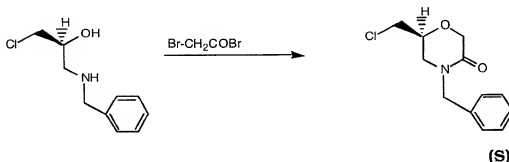
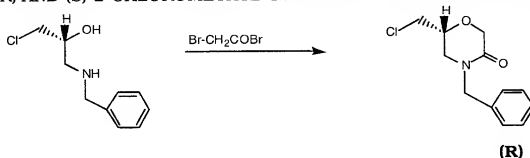
15 A mixture of (R)- epichlorohydrin (5g, 54.03 mmoles) and benzylamine (5.8g,54.03 mmoles) in cyclohexane (50 mL) was stirred at room temperature for 16 h. The resulting precipitates

were collected to give the title compound (5.4g, 50.09%): δ_{H} (DMSO-
 d_6) 2.28 (bs, 1H), 2.43- 2.67 (m, 2H), 3.45-3.85 (m, 5H), 5.13 (bs,
 1H), 7.05-7.48 (m, 5H).

In a similar manner (S) isomer was prepared from (S)-
 5 epichlorohydrin in 67% yield.

Step B

(R) AND (S)-2-CHLOROMETHYL-4-BENZYL-5-OXOMORPHOLINES



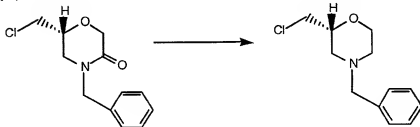
10

To a mixture of the title compound from step A above (5.3g,
 26.57 mmoles), NaOH (10.62g, 265 mmoles) CHCl_3 (50mL) and H_2O
 (20mL) was added dropwise a solution of bromoacetyl bromide
 15 (14.98g, 74.25 mmoles) in CHCl_3 (15mL) over a period of 1h at 0°C
 and then at room temperature for 16h. The organic layer was
 separated and washed successively with water, 1NHCl, and brine.
 The solvent evaporated to leave the title compound ((R) isomer)
 (5.43g, 84.4%): FABMS ($\text{M}+1$) =240 ; δ_{H} (CDCl_3) 3.2-3.33 (m,2H).
 20 3.50 (dd, 1H), 3.51 (dd, 1H), 4.0 (m,1H), 4.25 (d, 1H), 4.4 (d, 1H),
 4.52 (d, 1H), 4.7 (d, 1H), 7.20-7.33 (m, 5H),

In a similar manner (S) isomer was prepared (67 %). FABMS
 ($\text{M}+1$) = 240; δ_{H} (CDCl_3) 3.2-3.33 (m,2H). 3.50 (dd, 1H), 3.51 (dd,
 1H), 4.0 (m,1H), 4.25 (d, 1H), 4.4 (d, 1H), 4.52 (d, 1H), 4.7 (d, 1H),
 25 7.20-7.33 (m, 5H).

Step C

(R) -2-CHLOROMETHYL-4-BENZYL-MORPHOLINES



(R)

5

A solution of the title compound from Step B (5.09g, 21.23 mmoles) in anhydrous THF (55 mL) was added to a stirred 1.0M BH_3 -THF complex (109 mL) over a period of 0.5h at -15°C under nitrogen atmosphere. The mixture was stirred at room temperature for 1h, heated to reflux overnight and then cooled to 0°C . After concentrated HCl (75mL) was added to the reaction mixture, THF was evaporated *in vacuo*. The resulting aqueous solution was basified with 10% NaOH and extracted with CH_2Cl_2 . The extract was successively washed with water and brine, and the CH_2Cl_2 was evaporated to leave a crude product, which was chromatographed on silica gel with CH_2Cl_2 -2% acetone to give the title compound (3.2 g, 80%). FABMS ($M+1$) = 226, δ_{H} (CDCl_3) 2.1 (dd, 1H), 2.3 (dd, 1H), 2.72 (m, 1H), 2.84 (m, 1H), 3.5-3.6 (s, 2H), 3.62- 3.98 (m, 31H), 7.2-7.4 (m, 5H).

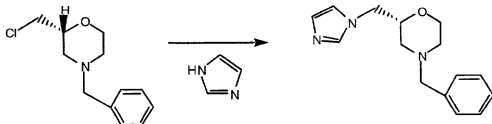
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Step D

(R)-4-BENZYL-2-(1H-IMIDAZOL-YL)METHYL-MORPHOLINES



5

(R)

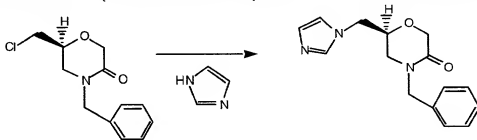
A solution of the title compound from Step C (3.1g, 13.77 mmol) in DMF (15 mL) was added to a stirred solution of NaH (1.29g 53.75 mmol) and imidazole (3.67g, 53.97 mmol) in DMF (50mL) under nitrogen atmosphere. The mixture was stirred at 60° C for 16h. DMF was evaporated *in vacuo*. The resulting crude product was extracted with CH₂Cl₂ and the extract was successively washed with water and brine, and the CH₂Cl₂ was evaporated to leave a crude product, which was chromatographed on silica gel with CH₂Cl₂-5 % (10% NH₄OH in methanol) to give the title compound (1.65 g, 45%). FABMS (M+1) = 258 (MH⁺); δ_H (CDCl₃) 1.8 (m, 1H), 2.15 (m, 1H), 2.8 (m, 2H), 3.4-3.8 (m, 7H), 6.9 (s, 1H), 7.02 (s, 1H), 7.3 (m, 5H), 7.5 (s, 1H).

10

15

Step E

(S)-4-BENZYL-2-(1H-IMIDAZOL-YL)METHYL-5-OXOMORPHOLINES



(S)

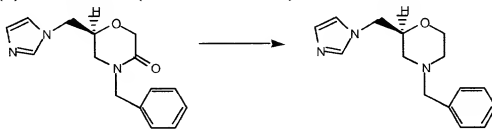
A solution of the title compound from Step B (2.73g, 11.37 mmol) in DMF (15 mL) was added to a stirred solution of NaH (1.55g 22.79 mmol) and imidazole 0.55g, 22.75 mmol) in DMF (25 mL) under nitrogen atmosphere. The mixture was stirred at 60°

25

C for 16h. DMF was evaporated *in vacuo*. The resulting crude product was extracted with CH_2Cl_2 and the extract was successively washed with water and brine, and the CH_2Cl_2 was evaporated to leave a crude product, which was chromatographed on silica gel with CH_2Cl_2 -5 % (10% NH_4OH in methanol) to give the title compound (0.761 g, 24.7%). FABMS ($M+1$) = 272 (MH^+); δ_{H} (CDCl_3) 3.12 (m, 2H), 3.98-4.71 (m, 7H), 6.98 (s, 1H), 7.1 (s, 1H), 7.2-7.4 (m, 5H), 7.98 (s, 1H).

10 Step F

(S)-4-BENZYL-2-(1H-IMIDAZOL-YL)METHYL-MORPHOLINES

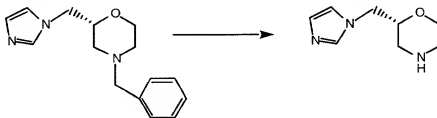


1 N LAH in ether (5.5 mL) was added to a stirred solution of the title compound (0.75g, 2.75 mmole) from step E in anhydrous

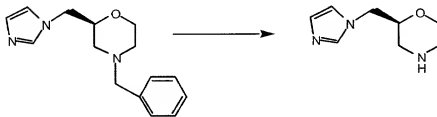
- 15 THF (25 mL) dropwise over a period of 0.5h and the resulting mixture was refluxed for 4h. The reaction mixture was slowly decomposed with ice-water and extracted with CH_2Cl_2 . The extract was washed with water and brine and dried (MgSO_4), filtered and evaporated to dryness to give the title compound (0.53g, 75%).
- 20 FABMS ($M+1$) = 258 δ_{H} (CDCl_3) 1.8 (m, 1H), 2.15 (m, 1H), 2.8 (m, 2H), 3.4-3.8 (m, 7H), 6.9 (s, 1H), 7.02 (s, 1H), 7.3 (m, 5H), 7.5 (s, 1H).

Step G

(R) AND (S)-[2-(1H-IMIDAZOL--1-YL)METHYL]MORPHOLINES



(R)



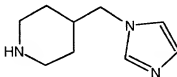
(S)

A mixture of the title compound (1.6g) from Step D and $\text{Pd}(\text{OH})_2$ on carbon (0.32g) in EtOH (20 mL) was stirred at 50 psi under an atmosphere of hydrogen for 24h. The catalyst was filtered to give the title compound (1.03g, 99.9%). FABMS ($M+1$) = 168 ; δ_{H} (CDCl_3) 2.4- 2.5 (m, 1H), 2.8 (m, 3H), 3.5 - 3.9 (m, 5H), 6.9 (s, 1H), 7.02 (s, 1H), 7.45 (s, 1H).

In a similar manner (S) isomer was prepared from (0.5g) and $\text{Pd}(\text{OH})_2$ on carbon (0.2g) in 99% yield. FABMS ($M+1$) = 168 ; δ_{H} (CDCl_3) 2.4- 2.5 (m, 1H), 2.8 (m, 3H), 3.5 - 3.9 (m, 5H), 6.9 (s, 1H), 7.02 (s, 1H), 7.45 (s, 1H).

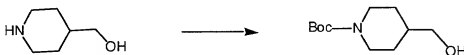
PREPARATIVE EXAMPLE 49

[4-(1H-IMIDAZOL--1-YL)METHYL]PIPERIDINE



Step A

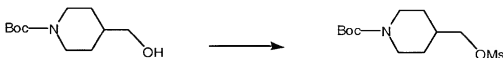
1N-tert-BUTOXYCARBONYL-4-HYDROXYMETHYL - PIPERIDINE



To a solution of 4-hydroxymethyl-piperidine (5g, 43.41
 5 mmoles) and triethylamine (8.78g, 86.82 mmoles) in CH_2Cl_2
 (100mL), di-tert-butylidicarbonate (18.95g, 86.82 mmoles) was
 added and stirred at room temperature for 16h. The solution was
 diluted with CH_2Cl_2 and washed with water, dried (MgSO_4) filtered
 and evaporated to give the title compound (9.04g, 99%). FABMS
 10 $(\text{M}+1) = 216$.

Step B

1N-tert-BUTOXYCARBONYL-4-METHANESULFONYLOXYMETHYL-
 PIPERIDINE

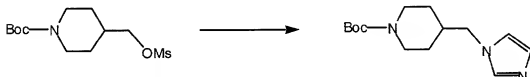


The title compound from Step A above (8.8g, 40.87 mmoles)
 and triethylamine (8.55 mL, 61.31 mmoles) were dissolved in CH_2Cl_2
 (100 mL) and the mixture was stirred under nitrogen at 0°C .
 Methanesulfonylchloride (3.8 mL mL, 49.05 mmoles) was added
 20 and the solution was stirred at room temperature for 2h. The
 solution was diluted with CH_2Cl_2 and washed with saturated
 aqueous sodium bicarbonate, water and dried (MgSO_4), filtered and
 evaporated to dryness to give the title compound (12.8g) FABMS
 (M+1) = 294.3.

25

Step C

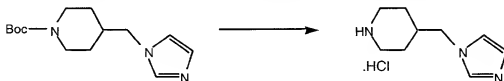
1N-tert-BUTOXYCARBONYL-4-(1H-IMIDAZOL-1-YL)METHYL-PIPERIDINE



- 5 A solution of the title compound from Step B (1.0g, 3.408 mmol) in DMF (15 mL) was added to a stirred solution of NaH (0.27g, 6.817 mmol) and imidazole (0.464g, 6.817 mmol) in DMF (15 mL) under nitrogen atmosphere. The mixture was stirred at 60° C for 16h. DMF was evaporated *in vacuo*. The resulting
- 10 crude product was extracted with CH₂Cl₂ and the extract was successively washed with water and brine, and the CH₂Cl₂ was evaporated to leave the title residue which was chromatographed on silica gel using 3% (10% conc NH₄OH in methanol)- CH₂Cl₂ as eluant to give the title compound (0.823 g). FABMS (M+1) = 266.2, δ_H
- 15 (CDCl₃) 0.8-1.0 (m, 2H), 1.2 (s, 9H), 1.2- 1.4 (m, 1H), 1.65 (m, 1H), 2.4 (dt, 2H), 3.6 (d, 2H), 4.8 (d, 2H), 6.7 (s, 1H), 6.8 (s, 1H), 7.2 (s, 1H).

Step D

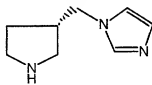
20 4-(1H-IMIDAZOL-1-YL)METHYL-PIPERIDINE



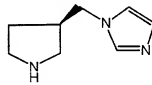
- The title compound(0.187g, 0.705 mmol) from Step C was stirred in 4N HCl in dioxane (20 mL) for 2h and then evaporated to
- 25 dryness to give the title compound which was used to couple with the tricyclic acid.

- 100 -
PREPARATIVE EXAMPLE 50

3(R) AND 3(S)-(1H-IMIDAZOL-1-YL)METHYL]PYRROLIDINES



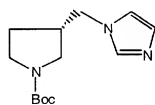
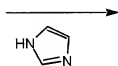
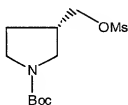
(R)



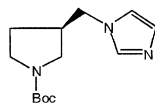
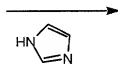
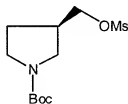
(S)

5 Step A

1N-tert-BUTOXYCARBONYL-3(R) AND 3(S) -(1H-IMIDAZOL-1-YL)
 METHYL] PYRROLIDINES



(R)



(S)

10

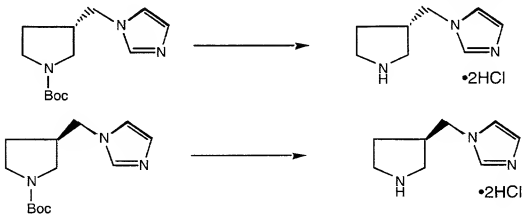
3(R)-(3-Methanesulfonyloxymethyl)pyrrolidine (J. Med. Chem. 1990, 33, 77-77) (0.993g, 3.56 mmoles) was dissolved in anhydrous DMF (25 mL) and sodium imidazole (0.6g, 10 mmoles) was added. The mixture was heated at 60° C for 2h and then evaporated to dryness. The product was extracted with CH₂Cl₂ and washed with brine. CH₂Cl₂ extract was evaporated to dryness to give the titled compound (1.1409g, 100%), ESMS: FABMS (M+1) = 252; δ_H (CDCl₃) 1.45 (s, 9H), 1.5-1.7 (m, 1H), 1.9 - 2.1 (m, 1H), 2.5-2.7 (m, 1H), 3.0-3.2 (m, 1H), 3.3- 3.6 (m, 2H), 3.9 (dd, 2H), 6.9 (s, 1H), 7.1(s, 1H), 7.45 (s, 1H)

20

In a similar manner, (S) isomer was prepared from 3(S)-(3-Methanesulfonyloxymethyl)pyrrolidine (0.993g, 3.56 mmoles) to give the title compound (1.1409g, 100%).

Step B

3(R) AND 3(S)-(1H-IMIDAZOL--1-YL)METHYL)PYRROLIDINES

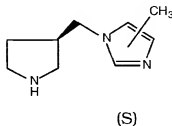


The title compound(0.48g, 1.91 mmole) from Step A was stirred in 4N HCl in dioxane (10 mL) for 2h and then evaporated to dryness to give the title compound which was used to couple with the tricyclic acid.

In a similar manner (S) isomer was prepared.

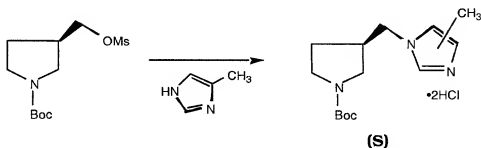
PREPARATIVE EXAMPLE 51

3(S)-(1H-4 (5)-METHYLIMIDAZOL--1-YL)METHYL)PYRROLIDINE



Step A

1N-tert-BUTOXYCARBONYL- 3(S) -(1H-4 (5)-METHYLIMIDAZOL -I-YL) METHYL) PYRROLIDINE



3(S)-(3-Methanesulfonyloxymethyl)pyrrolidine (1.05g, 3.77 mmole) was dissolved in anhydrous DMF (25 mL) and sodium 4-

methylimidazole (0.74g, 10 mmoles) was added. The mixture was heated at 60° C for 2h and then evaporated to dryness. The product was extracted with CH_2Cl_2 and washed with brine. CH_2Cl_2 was evaporated to dryness to give the titled compound

5 (0.92g, 100%), FABMS (M+1) = 266.

Step B

3(S)-(1H-4 (5)-METHYLIMIDAZOL -1-YL)METHYL]PYRROLIDINE

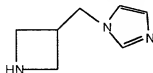


10 The title compound(0.31g, 1.17 mmoles) from Step A was stirred in 4N HCl in dioxane (10 mL) for 2h and then evaporated to dryness to give the title compound which was used to couple with the tricylic acid.

15

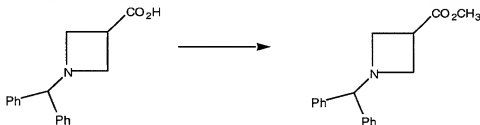
PREPARATIVE EXAMPLE 52

3-(1H-IMIDAZOL-1-YL)METHYL-PYRROLIDINE



Step A

1N-DIPHENYLMETHYL-AZETIDINE-4-METHYLCARBOXYLATE



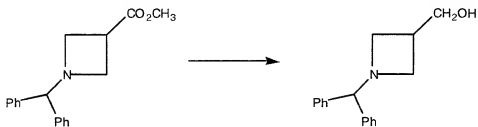
20

1N-Diphenylmethyl-azetidine-3-carboxylic acid (J. Chem. Res. 1996, 430) (5.38g, 20.16 mmoles) was refluxed with conc. H_2SO_4 (2mL) and MgSO_4 (5g) in anhydrous methanol (25 mL) for 16h. Evaporated to dryness and the residue was extracted with

ethylacetate and washed the extract with 10% sodiumbicarbonate and water. Ethylacetate was evaporated to give a residue which was chromatographed on silica gel using hexane-10% ethylacetate as the eluant afforded the title compound (2.2g, 40.64%), FABMS
 5 (M+1) = 282; δ_H (CDCl₃) 3.2- 3.6 (m, 5H), 3.7 (s, 3H), 4.45 (s, 1H), 7.2 - 7.4 (m, 10H).

Step B

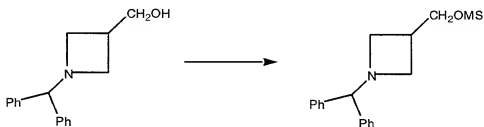
1N-DIPHENYLMETHYL-3-HYDROXYMETHYL-AZETIDINE



1 N LAH in ether (20 mL) was added to a stirred solution of the title compound (2g, 7.11 mmole) from Step A in anhydrous ether (25 mL) dropwise over a period of 0.5h and the resuting mixture was refluxed for 4h. The reaction mixture was slowly
 15 decomposed with ice-water and extracted with ethylacetate. The extract was washed with with water and brine and dried (MgSO₄), filtered and evaporated to dryness to give title compound (1.72g, 98%). FABMS (M+1) = 254 .

Step C

1N-DIPHENYLMETHYL-3-METHANESULFONYLOXYMETHYL - AZETIDINE

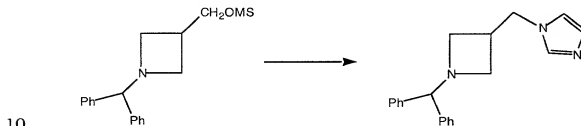


The title compound from Step B above (1.7g, 6.72 mmoles) and triethylamine (1.1g, 10.87 mmoles) were dissolved in CH₂Cl₂ (20 mL) and the mixture was stirred under nitrogen at 0°C .

Methanesulfonylchloride (1.1g, 9.6 mmoles) was added and the solution was stirred at room temperature for 2h. The solution was diluted with CH_2Cl_2 and washed with saturated aqueous sodium bicarbonate, water and dried (MgSO_4), filtered and evaporated to dryness to give the title compound (2.32g, 99%). FABMS ($\text{M}+1$) = 332.

Step D

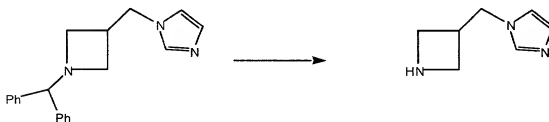
1N-DIPHENYLMETHYL-3-(1H-IMIDAZOL-1YL)METHYL -AZETIDINE



A solution of the title compound from Step C (2.3g, 6.95 mmoles) in DMF (15 mL) was added to a stirred solution of NaH (0.25g, 10.42 mmoles) and imidazole (0.71g, 10.44 mmoles) in DMF (10 mL) under nitrogen atmosphere. The mixture was stirred at 60° C for 16h. DMF was evaporated *in vacuo*. The resulting crude product was extracted with CH_2Cl_2 and the extract was successively washed with water and brine, and the CH_2Cl_2 was evaporated to leave the title compound (2.1 g, 100%). FABMS ($\text{M}+1$) = 304

20 Step E

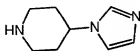
3-(1H-IMIDAZOL-1-YL)METHYL-PYRROLIDINE



A mixture of the title compound (1.7g) from Step D and $\text{Pd}(\text{OH})_2$ on carbon (0.2g) in EtOH (20 mL) was stirred at 50 psi under an atmosphere of hydrogen for 24h. The catalyst was filtered to give the title compound (0.508g, 66.8%). m/z = 137 (MH^+)

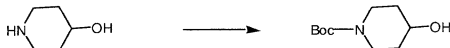
- 105 -
PREPARATIVE EXAMPLE 53

4-(1H-IMIDAZOL-1-YL) -PIPERIDINE



Step A

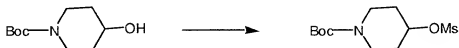
- 5 1N-tert-BUTOXYCARBONYL-4-HYDROXY - PIPERIDINE



- To a solution of 4-hydroxy-piperidine (2g, 19.78 mmoles) and triethylamine (4.16 mL, 29.67 mmoles) in CH_2Cl_2 (20mL), di-tert-butylidicarbonate (5.18g, 23.72 mmoles) was added and stirred at room temperature for 16h. The solution was diluted with CH_2Cl_2 and washed with water, dried(MgSO_4) filtered and evaporated to give the title compound (3.95g, 99%). FABMS ($\text{M}+1$) = 202.
- 10

Step B

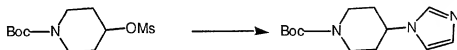
- 15 1N-tert-BUTOXYCARBONYL-4-METHANESULFONYLOXY-PIPERIDINE



- The title compound from Step A above (3.5g, 17.39 mmoles) and triethylamine (4.85mL, 34.79 mmoles) were dissolved in CH_2Cl_2 (30 mL) and the mixture was stirred under nitrogen at 0°C . Methanesulfonylchloride (1.62 mL, 20.88 mmoles) was added and the solution was stirred at room temperature for 2h. The solution was diluted with CH_2Cl_2 and washed with saturated aqueous sodium bicarbonate, water and dried (MgSO_4), filtered and evaporated to dryness to give the title compound (4.68g, 96.4 %).
- 25 ESMS: m/z = 280 (MH^+)

Step C

1N-tert-BUTOXYCARBONYL-4-(1H-IMIDAZOL-1-YL) -PIPERIDINE



- A solution of the title compound from Step B (4.0g, 14.32
 5 mmoles) in DMF (120 mL) was added to a stirred solution of NaH (0.52g, 21.66 mmoles) and imidazole (1.46g, 21.47 mmoles) in DMF (20 mL) under nitrogen atmosphere. The mixture was stirred at 60° C for 16h. DMF was evaporated *in vacuo*. The resulting crude
 10 product was extracted with CH₂Cl₂ and the extract was successively washed with water and brine, and the CH₂Cl₂ was evaporated to leave the title residue which was chromatographed on silica gel using 3% (10% conc NH₄OH in methanol)- CH₂Cl₂ as eluant to give the title compound (0.94 g, 26%). FABMS (M+1) = 252; δ_H (CDCl₃) 1.4 (s, 9H), 1.6-1.8 (m, 2H), 2.0 (dd, 2H), 2.8 (dt, 2H), 4.05 (m, 1H),
 15 4.2 m, 2H), 6.9 (s, 1H), 7.0 (s, 1H), 7.65 (s, 1H).

Step D

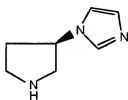
4-(1H-IMIDAZOL-1-YL) -PIPERIDINE



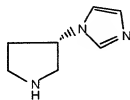
- The title compound(0.21g, 0.836 mmoles) from Step C was
 20 stirred in 4N HCl in dioxane (5 mL) for 2h and then evaporated to dryness to give the title compound which was used to couple with the tricyclic acid.

PREPARATIVE EXAMPLE 54

3-(R) AND (S)-(1H-IMIDAZOL-1-YL) -PYRROLIDINES



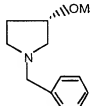
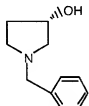
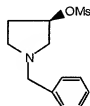
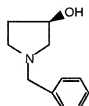
(R)



(S)

5 Step A

1N-BENZYL-3-(R) AND (S)-METHANESULFONYLOXY)-
PYRROLIDINES

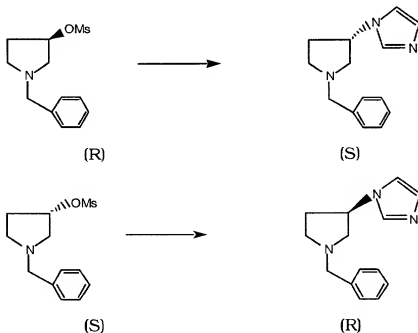


- 10 1N-Benzyl-3(R) -hydroxy -pyrrolidines (5g, 28.21 mmoles) and triethylamine (7.86 mL, 56.35 mmoles) were dissolved in CH_2Cl_2 (50 mL) and the mixture was stirred under nitrogen at 0°C .
- Methanesulfonylchloride (2.62 mL, 33.87 mmoles) was added and the solution was stirred at room temperature for 2h. The solution
- 15 was diluted with CH_2Cl_2 and washed with saturated aqueous sodium bicarbonate, water and dried (MgSO_4), filtered and evaporated to dryness to give the title compound (7.2g, 96.4 %).
- FABMS ($\text{M}+1$) = 256; δ_{H} (CDCl_3) 2.2 (m, 1H), 2.3 (m, 1H), 2.52 (m, 1H), 2.7-2.85 (m, 3H), 2.95 (s, 3H), 3.65 (q, 2H), 5.16 (m, 1H), 7.3
- 20 (s, 5H).

In a similar way (S) isomer was prepared from 1N-Benzyl-3(S)-hydroxy-pyrrolidines (5g, 28.21 mmoles) to give the title compound (7.15g, 98%)

Step B

1N-BENZYL-3-(S) AND (R)-(1H-IMIDAZOL-1-YL) - PYRROLIDINES

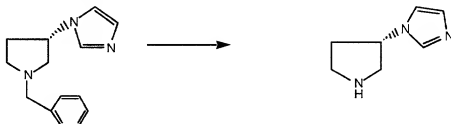


5 A solution of the title compound from Step A (2.0g, 7.84 mmoles) was added to a stirred solution imidazole (1.1g, 16.17 mmoles) in DMF (25 mL) under nitrogen atmosphere. The mixture was stirred at 60° C for 16h. DMF was evaporated *in vacuo*. The resulting crude product was extracted with CH₂Cl₂ and the extract was successively washed with water and brine, and the CH₂Cl₂ was evaporated to leave the title residue which was chromatographed on silica gel using 3% (10% conc NH₄OH in methanol)- CH₂Cl₂ as eluant to give the title compound (0.95 g, 50.56%). FABMS (M+1) = 228.

In a similar fashion the other isomer was prepared.

Step C

3-(R) AND (S)-(1H-IMIDAZOL-1-YL) -PYRROLIDINES





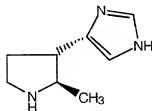
- A mixture of the title compound(0.95 g) from Step B and 10% Pd on carbon (0.5 g) in EtOH (20 mL) was stirred at 50 psi under an atmosphere of hydrogen for 24h. The catalyst was filtered to give the title compound (0.522 g, 99.9%) which was used to couple with the tricyclic acid.

In a similar manner (R) isomer was prepared from (1.0 g) and 10% Pd on carbon on carbon (0.6 g) in 99% yield.

10

PREPARATIVE EXAMPLE 55

(-) 2-METHYL-3-(1H-IMIDAZOL-4-YL) -PYRROLIDINE

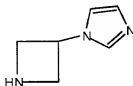


This compound was prepared according to the procedure in J. Med. Chem. 1995, 1593-1599.

15

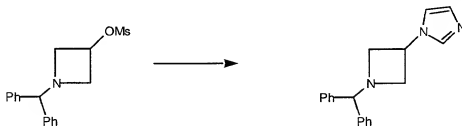
PREPARATIVE EXAMPLE 56

3-(1H-IMIDAZOL-1-YL) -AZETIDINE



Step A

1N-DIPHENYLMETHYL-(1H-IMIDAZOL-1-YL)-AZETIDINE

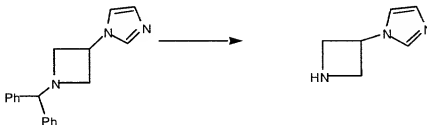


1N-Diphenylmethyl-3-methanesulfonyloxy-azetidine (J. Che.

- 5 Res. 1996, 430) (10.0g, 29.26 mmoles) was added to a stirred solution imidazole (5.96g, 87.78 mmoles) in DMF (100 mL) under nitrogen atmosphere. The mixture was stirred at 60° C for 16h. DMF was evaporated *in vacuo*. The resulting crude product was extracted with CH_2Cl_2 and the extract was successively washed with
- 10 water and brine, and the CH_2Cl_2 was evaporated to leave the title residue which was chromatographed on silica gel using 4 % (10% conc NH_4OH in methanol)- CH_2Cl_2 as eluent to give the title compound (2.87 g, 33.9 %). FABMS ($M+1$) = 290; δ_{H} (CDCl_3) 3.3 (dd, 2H), 3.65 (dt, 2H), 4.45 (s, 1H), 4.8 (m, 1H), 7.1-7.5 (m, 12H),
- 15 7.8 (s, 1H).

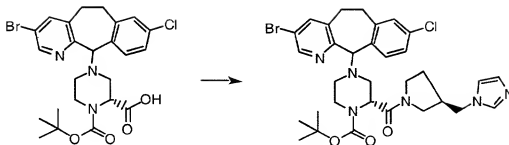
Step B

3-(1H-IMIDAZOL-1-YL)-AZETIDINE



- 20 A mixture of the title compound(2.8g) from Step A and 10% Pd on carbon (1.1g) in MeOH (25 mL) was stirred at 50 psi under an atmosphere of hydrogen for 24h. The catalyst was filtered to give the title compound (1.05 g, 99.9%) which was used to couple with the tricyclic acid.

- 111 -
EXAMPLE 54

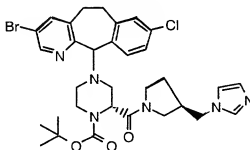


- 4-(3-bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-1-[(1,1-dimethylethoxy)carbonyl]-2(R)-piperazinecarboxylic acid (2g, 3.8 mmol.) was added to a solution of the title compound from Preparative Example 50 (1.1g, 4.7 mmol), DEC (1.8g, 9.4 mmol.), HOBT (1.28g, 9.48 mmol.) and NMM (2.6 mL, 23.7 mmol.) in DMF (100 mL). The resulting solution was stirred at room temperature 24 hours. The reaction mixture was diluted with H₂O until precipitation ceased and the slurry filtered. The precipitate was diluted with CH₂Cl₂, washed with brine, dried over Na₂SO₄ and concentrated. The crude product was purified by flash chromatography using a 5% (10%NH₄OH in MeOH) solution in CH₂Cl₂ as eluent to give the title compound (1.48g, 55 % yield). FABMS (M+1)= 669.

EXAMPLE 55 and EXAMPLE 56

- The title compound from Example 1 was separated into individual 11-(R)- and 11-(S)- isomers by Preparative HPLC with a CHIRALPAK AD column using a 15% iPrOH in hexane solution with 0.2% DEA as eluant.

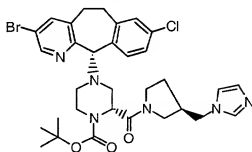
EXAMPLE 55



- 112 -

Isomer A: retention time (analytical) = 8.885 minutes; $[\alpha]_D = -13.1$ (3.06 mg in 2.0 mL MeOH); FABMS (M+1)= 669.

EXAMPLE 56



Isomer B: retention time (analytical) = 8.885 minutes; $[\alpha]_D = +12.1$ (2.32 mg in 2.0 mL MeOH); FABMS (M+1)= 669.

EXAMPLE 57-69

By essentially the same procedure set forth in Example 1 only substituting the appropriate amines, one can obtain compounds of the formula shown below wherein R^8 is defined in Table 9 below.

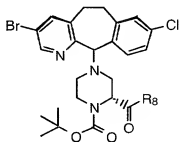


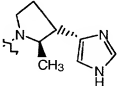

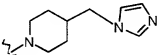
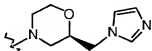


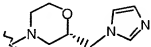
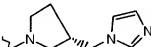

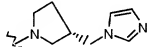
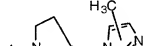
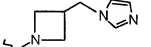
TABLE 9

Ex.	R^8	CMPD
57	 11-(R,S)	FABMS (M+1)= 669

- 113 -
TABLE 9 - continued

Ex.	R ⁸	CMPD
58		FABMS (M+1)= 655
59		FABMS (M+1)= 655
60		FABMS (M+1)= 669
61		FABMS (M+1)= 641
62		FABMS (M+1)= 683
63		FABMS (M+1)= 685

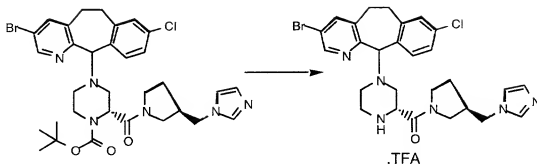
- 114 -
TABLE 9 - continued

Ex.	R ^B	CMPD
64	 11- (R,S)	FABMS (M+1)= 685
65	 11- (R,S)	FABMS (M+1)= 669
66	 11-S	FABMS (M+1)= 669
67	 11-R	FABMS (M+1)= 669
68	 11- (R,S)	FABMS (M+1)= 683
69	 11- (R,S)	FABMS (M+1)= 655

10028251.122001

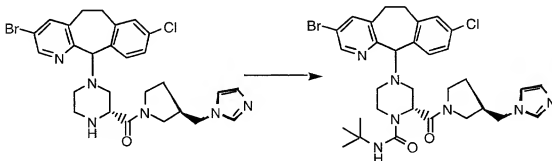
- 115 -
EXAMPLE 70

Step A



- 5 The title compound from Example 54 (0.1g, 0.15 mmoles) was stirred at room temperature in CH_2Cl_2 (20 mL) and TFA (1 mL) for 2h. The reaction mixture was evaporated to dryness to give the title compound which was used as such in Step B below.

Step B



- 10 The title compound from Step A (0.186g, 0.182 mmoles) dissolved in CH_2Cl_2 (20 mL) and triethyl amine (0.063 g, 0.621 mmoles) and t-butylisocyanate (0.0185g, 0.187 mmoles) was added. The resulting solution was stirred at room temperature for 15 2 h, diluted with water and extracted with CH_2Cl_2 . CH_2Cl_2 extract was dried (MgSO_4) and filtered and concentrated in CH_2Cl_2 as eluant to give the title compound (0.084g) FABMS ($\text{M}+1$)= 668.

EXAMPLES 71-73

- 20 By essentially the same procedure set forth in Example 1 only substituting with different isocyanates, one can obtain compounds of the formula shown below wherein R^9 is as defined in Table 10 below.

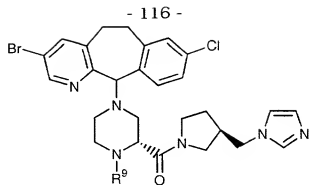


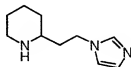
TABLE 10

R ⁹	CMPD
Ex. 71 11- (R,S)	FABMS (M+1)= 668
Ex. 72 11- (R,S)	FABMS (M+1)= 696
Ex. 73 11- (R,S)	FABMS (M+1)= 710

5

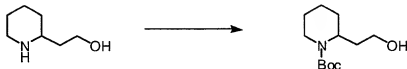
PREPARATIVE EXAMPLE 57

2(R/S)-[2-(1H-IMIDAZOL-1-YL)ETHYL]PIPERIDINE



Step A

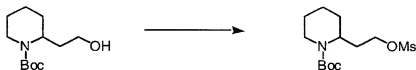
1N-tert-BUTOXYCARBONYL-2(R/S)-(2-HYDROXYETHYL)-
PIPERIDINE



- 5 2(R/S)-(2-Hydroxyethyl)piperidine (5g, 38.7mmoles) and sodium hydroxide (1.55g, 67.4mmoles) were dissolved in THF-water (1:1) (100mL) and di-tert-butylidicarbonate (9.29g, 42.6mmoles) was added and the mixture was stirred at 25°C for 120h. The solution was treated with BioRad 50W-X4 (RSO₃H) resin (42mL) and filtered.
- 10 The resin was washed with water and THF and the combined filtrates were evaporated to dryness. Chromatography on silica gel using 1% (10% conc. NH₄OH in methanol)-dichloromethane as the eluant afforded the title compound (8.87g, 95%): CIMS: m/z 230.2 (MH⁺); δ_H (CDCl₃) 1.47ppm (9H, s, CH₃); δ_C (CDCl₃) CH₃: 28.4, 28.4, 28.4; CH₂: 19.2, 25.6, 29.6, 32.3, ~39.6, ~58.3; CH: ~45.9; C: 80.1, carbonyl not visible.

Step B

1N-tert-BUTOXYCARBONYL-2(R/S)-(2-METHANESULFONYLOXYETHYL)PIPERIDINE



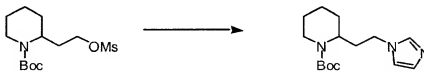
- 20 The title compound from Step A above (2g, 8.72mmoles) and triethylamine (7.29mL; 52.4mmoles) were dissolved in dichloromethane (50mL) and the mixture was stirred under argon at 0°C. Methanesulfonyl chloride (2.03mL; 26.2mmoles) was added and the solution was stirred at 25°C for 2h. The solution was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate, water and dried (MgSO₄), filtered and evaporated to dryness. The product was chromatographed on silica
- 25

gel using 2% (10% conc. NH_4OH in methanol)-dichloromethane as the eluant to give the title compound (1.25g, 61%); ESMS: m/z 308.1 (MH^+); δ_c (CDCl_3) 28.5, 28.5, 28.5, 37.4/39.3; CH_2 : 19.1, 23.8/25.5, 28.9/29.6, 33.1, 45.2; CH: 54.2; C: 79.8, ~155.2.

5

Step C

1N-tert-BUTOXYCARBONYL-2(R/S)-[2-(1H-IMIDAZOL-1-YL)ETHYL]PIPERIDINE

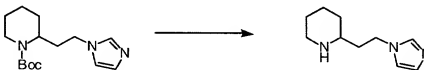


- 10 The title compound from Step B above (2.68g, 8.72mmoles) (crude product, prior to chromatography) was dissolved in anhydrous DMF (30mL) and sodium imidazole (1.18g, 13.1mmoles) was added. The mixture was heated at 70°C for 2h and then evaporated to dryness. The product was directly chromatographed
- 15 on silica gel using 1% (10% conc. NH_4OH in methanol)-dichloromethane as the eluant to give the title compound (1.69g, 69%); ESMS: m/z 280.1 (MH^+); d_H (CDCl_3) 1.48ppm (9H, s, CH_3); d_c (CDCl_3) CH_3 : 28.5, 28.5, 28.5; CH_2 : 19.1, 25.5, 28.9, 31.8, ~39.1, 44.3; CH: 48.1, 118.9, 129.5, 137.1; C: 80.1, carbonyl not visible.

20

Step D

2(R/S)-[2-(1H-IMIDAZOL-1-YL)ETHYL]PIPERIDINE



- 25 The title compound from Step C above (1.6g, 5.73mmoles) was dissolved in methanol (10mL) and 10% conc. H_2SO_4 in dioxane (v/v) (40mL) was added and the solution was stirred at 25°C for 2h. The mixture was treated with BioRad AG1-X8 (OH) resin until basic. The resin was filtered off and washed with methanol. The combined filtrates were evaporated to dryness and the product was

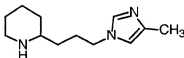
chromatographed on silica gel using 5% (10% conc. NH_4OH in methanol)-dichloromethane as the eluant to give the title compound

(1.02g, 99%): CIMS: m/z 180.35 (MH^+); δ_{H} (CDCl_3) 6.94 (1H, s, Im- H_j), 7.18 (1H, s, Im- H_d) and 7.50ppm (1H, s, Im- H_2); δ_{C} (CDCl_3) CH_2 :

5 24.6, 26.8, 33.2, 38.6, 43.8, 47.0; CH: 53.9, 118.9, 129.5, 118.8.

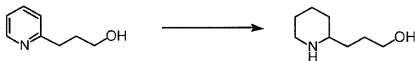
PREPARATIVE EXAMPLE 58

2(R/S)-[3-(1H-4-METHYLIMIDAZOL-1-YL)PROPYL]PIPERIDINE



10 Step A

2(R/S)-(3-HYDROXYPROPYL)PIPERIDINE



2-(3-Hydroxypropyl)pyridine (5g, 36.4mmoles) was dissolved in 1N HCl (36.4mL, 36.4mmoles) and water (63.6mL) and platinum

15 (IV) oxide monohydrate (1g, 4.08mmoles) was added under an argon atmosphere. The mixture was hydrogenated at 55psi in a Parr

bomb at 25°C for 96h. The catalyst was filtered off through Celite® and washed with water. The combined filtrates were treated with

20 and washed with water. The combined filtrates were evaporated to dryness and the product was chromatographed on silica gel using

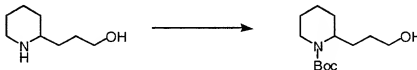
10% increasing to 20% (10% conc. NH_4OH in methanol)-dichloromethane as the eluant to give the title compound (5.22g,

100%): CIMS: m/z 144.40 (MH^+); δ_{C} (d_6 -DMSO) CH_2 : 24.0, 25.3,

25 28.8, 31.5, 32.8, 45.9, 60.8; CH: 56.1.

Step B

1N-tert-BUTOXYCARBONYL-2(R/S)-(3-HYDROXYPROPYL)
PIPERIDINE

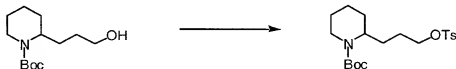


5 The title compound from Step A above (3g, 20.9mmoles) was reacted with di-tert-butylidicarbonate (5.03g, 23mmoles) and sodium hydroxide (0.8378g, 20.9mmoles) essentially as described in Preparative Example 57, Step A above, but allowing the reaction to proceed for 166h. The product was chromatographed on silica gel
10 using 3% (10% conc. NH_4OH in methanol)-dichloromethane as the eluant to give the title compound (4.04g, 79%); ESMS: m/z 244.0 (MH^+); δ_{H} (CDCl_3) 1.45ppm (9H, s, CH_3); δ_{C} (CDCl_3) CH_3 : 28.5, 28.5, 28.5; CH_2 : 19.0, 25.6, 26.2, 29.2, ~38.8, 62.8; CH: ~50.0; C: 79.3, ~155.2.

15

Step C

1N-tert-BUTOXYCARBONYL-2(R/S)-[3-(4-TOLUENESULFONYLOXY)PROPYL]PIPERIDINE



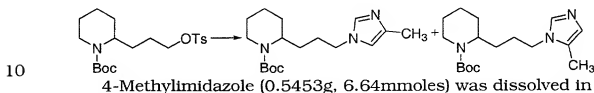
20 The title compound from Step B above (2g, 8.22mmoles) was dissolved in anhydrous pyridine (10mL) and the solution was cooled with stirring to 0°C . 4-Toluenesulfonyl chloride (1.88g, 9.86mmoles) was added and the mixture was stirred at 0°C for 2h. The mixture was evaporated to dryness and the residue was taken up in
25 dichloromethane and washed with saturated aqueous sodium bicarbonate, water, dried (MgSO_4), filtered and evaporated to dryness. The product was chromatographed on silica gel using 0.25% methanol in dichloromethane as the eluant to give the title compound (2.53g, 77%); ESMS: m/z 398.1 (MH^+).

- 121 -

- δ_{H} (CDCl_3) 1.41 (9H, s, CH_3), 2.45 (3H, s, Ar- CH_3), 4.06 (2H, m, CH_2O), 7.36 (2H, d, Ar- H_3 and Ar- H_5) and 7.79ppm (2H, m, Ar- H_2 and Ar- H_6); δ_{C} (CDCl_3) CH_3 : 19.1, 28.5, 28.5, 28.5; CH_2 : 21.7, 22.8, 25.7, 25.8, 28.8, 38.7, 70.6; CH: ~49.6, 127.9, 127.9, 129.9, 129.9; 5 C: 71.1, 133.2, 144.6, 155.1.

Step D

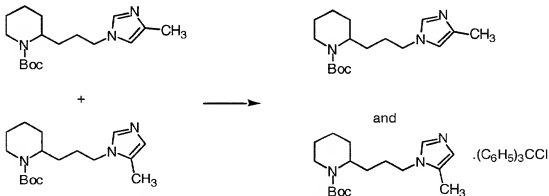
1N-tert-BUTOXYCARBONYL-2(R/S)-[3-(1H-4/5-METHYLIMIDAZOL-1-YL)PROPYL]PIPERIDINE



- anhydrous DMF(15mL) and 95% sodium hydride (0.1678g, 6.64mmoles) was added. The mixture was stirred at 25°C for 0.5h. under argon. The title compound from Preparative Example 58,
- 15 Step C, (2.4g, 6.04mmoles) in anhydrous DMF (10mL) was added and the mixture was stirred at 25°C for 1h. The product was worked up as described in Preparative Example 2, Step A and chromatographed on silica gel using 3% methanol in dichloromethane as the eluant to give a mixture of the title
- 20 compounds (1.459g, 79%) (4-Me:5-Me::63:37): CIMS; m/z 308.25 (MH^+); 4-Me: δ_{H} (CDCl_3) 1.43 (9H, s, CH_3), 2.18 (3H, s, Im-4-Me), 3.87 (2H, m, CH_2 -Im), 6.58 (1H, s, Im- H_5) and 7.33ppm (1H, s, Im- H_2); δ_{C} (CDCl_3) CH_3 : 13.8, 28.5, 28.5, 28.5; CH_2 : 19.0, 25.6, 26.4, 27.7, 28.7, 38.9, 46.5; CH: ~49.4, 115.2, 136.2; C: 79.4, 138.7, 155.1
- 25 and 5-Me: δ_{H} (CDCl_3) 1.43 (9H, s, CH_3), 2.16 (3H, s, Im-5-Me), 3.87 (2H, m, CH_2 -Im), 6.74 (1H, s, Im- H_4) and 7.37ppm (1H, s, Im- H_2); δ_{C} (CDCl_3) CH_3 : 9.3, 28.5, 28.5, 28.5; CH_2 : 19.0, 25.6, 26.5, 27.3, 28.7, 39.0, 44.4; CH: ~49.4, 126.9, 136.8; C: 79.4, ~138.7, 155.1.

Step E

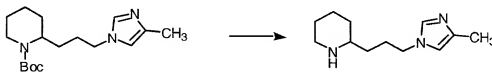
1N-tert-BUTOXYCARBONYL-2(R/S)-[3-(1H-4-METHYLIMIDAZOL-1-YL)PROPYL]PIPERIDINE



- 5 The mixture of compounds from Step D above (1.054g) was dissolved in anhydrous CH_2Cl_2 (10mL) at 0°C under argon. Trityl chloride (0.3891g, 1.1 equivalents per equivalent of the 5-methyl isomer) was added and the mixture was stirred at 0°C for 2h. The reaction mixture was introduced directly onto a silica gel column
- 10 and the column was eluted with 50% ethyl acetate in acetone to give the pure 4-methyl isomer (0.7242g, 69%): 4-Me: CIMS: m/z 308.30 (MH⁺); δ_{H} (CDCl₃) 1.43 (9H, s, CH₃), 2.18 (3H, s, Im-4-Me), 3.84 (2H, m, CH₂-Im), 6.58 (1H, s, Im-H₃) and 7.30ppm (1H, s, Im-H₂); δ_{C} (CDCl₃) CH₃: 13.8, 28.5, 28.5, 28.5; CH₂: 19.0, 25.5, 26.4, 27.7,
- 15 28.7, 38.8, 46.5; CH: ~49.4, 115.2, 136.2; C: 79.3, 138.4, 155.1.

Step F

2-(R/S)-[3-(1H-4-METHYLIMIDAZOL-1-YL)PROPYL]PIPERIDINE

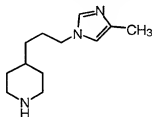


- 20 The title compound from Step E above (0.4456g, 1.5mmoles) was deprotected as described in Preparative Example 57, Step D and the product was chromatographed on silica gel using 20% (10% conc. NH_4OH in methanol)-dichloromethane as the eluant to give the title compound (0.2627g, 87%): CIMS: m/z 208.25 (MH⁺); δ_{H}
- 25 (CDCl₃) 2.14 (3H, s, Im-4-Me), 3.79 (2H, m, CH₂-Im), 6.52 (1H, s,

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Im-H₂) and 7.24ppm (1H, s, Im-H₂); δ_c (CDCl₃) CH₃: 13.7; CH₂: 24.7, 26.6, 27.5, 32.9, 34.3, 47.0, 47.1; CH: 56.3, 115.2, 136.1; C: 138.4.

PREPARATIVE EXAMPLE 59



5

Step A

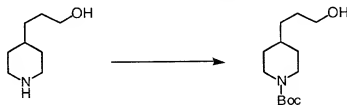
4(R/S)-(3-HYDROXYPROPYL)PIPERIDINE



4-(3-Hydroxypropyl)pyridine (5g, 36.4mmoles) was dissolved
10 in 1N HCl (36.4mL, 36.4mmoles) and water (63.6mL) and platinum
(IV) oxide monohydrate (1g, 4.08mmoles) was added under an argon
atmosphere. The mixture was hydrogenated at 55psi in a Parr
bomb at 25°C for 66h. The catalyst was filtered off through Celite®
and washed with water. The combined filtrates were treated with
15 BioRad AG1-X8 (OH) resin until basic. The resin was filtered off
and washed with water. The combined filtrates were evaporated to
dryness and the product was chromatographed on silica gel using
7% (10% conc. NH₄OH in methanol)-dichloromethane as the eluant
to give the title compound (4.91g, 94%); CIMS: m/z 144.40 (MH⁺); δ_c
20 (d₆-DMSO) CH₂: 29.4, 31.6, 31.6, 32.8, 45.1, 45.1, 60.8; CH: 34.8.

Step B

N-tert-BUTOXYCARBONYL-4(R/S)-(3-HYDROXYPROPYL)PIPERIDINE

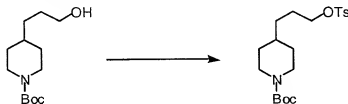


- 5 The title compound from Step A above (3g, 20.9mmoles) was reacted with di-tert-butylidicarbonate (5.03g, 23mmoles) and sodium hydroxide (0.8378g, 20.9mmoles) essentially as described in Preparative Example 57, Step A above, but allowing the reaction to proceed for 166h. The product was chromatographed on silica gel
- 10 using 3% (10% conc. NH_4OH in methanol)-dichloromethane as the eluant to give the title compound (3.33g, 65%); ESMS: m/z 244.2 (MH^+); δ_{H} (CDCl_3) 1.47ppm (9H, s, CH_3); δ_{C} (CDCl_3) CH_3 : 28.5, 28.5, 28.5; CH_2 : 29.9, 29.9, 32.2, 32.6, 44.1, 44.1; CH: 35.9; C: 79.3, ~154.8.

15

Step C

1N-tert-BUTOXYCARBONYL-4(R/S)-[3-(4-TOLUENESULFONYLOXY)PROPYL]PIPERIDINE



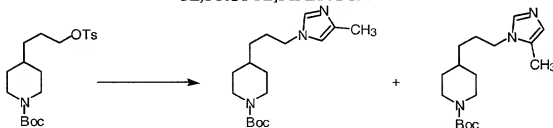
- 20 The title compound from Step B above (2g, 8.22mmoles) was dissolved in anhydrous pyridine (10mL) and the solution was cooled with stirring to 0°C . 4-Toluenesulfonyl chloride (1.88g, 9.86mmoles) was added and the mixture was stirred at 0°C for 2h. The mixture was evaporated to dryness and the residue was taken up in
- 25 dichloromethane and washed with saturated aqueous sodium bicarbonate, water, dried (MgSO_4), filtered and evaporated to dryness. The product was chromatographed on silica gel using

0.5% methanol in dichloromethane as the eluant to give the title compound (2.86g, 88%); ESMS: m/z 398.1 (MH⁺).

δ_H (CDCl₃) 1.44 (9H, s, CH₃), 2.46 (3H, s, Ar-CH₃), 4.01 (2H, m, CH₂O), 7.35 (2H, d, Ar-H₃ and H₉) and 7.79ppm (2H, d, Ar-H₂ and H₆); δ_C (CDCl₃) CH₃: 21.7, 28.6, 28.6, 28.6; CH₂: 26.1, 32.0, 32.0, 32.1, 43.9, 43.9, 70.7; CH: 35.5, 127.9, 127.9, 129.9, 129.9; C: 79.3, 133.1, 144.8, 154.9.

Step D

- 10 1N-tert-BUTOXYCARBONYL-4-[3-(1H-4/5-METHYLIMIDAZOL-1-
YL)PROPYL]PIPERIDINE

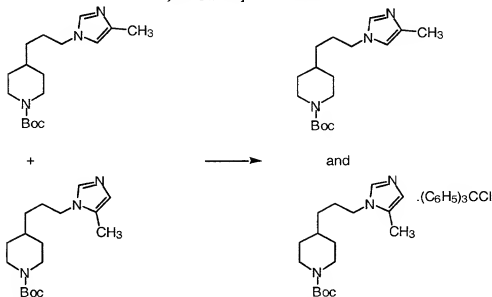


4-Methylimidazole (0.5453g, 6.64mmoles) was dissolved in anhydrous DMF (15mL) and 95% sodium hydride (0.1678g,

- 15 6.64mmoles) was added to the stirred solution at 25°C under argon. The solution was stirred at 25°C for 0.5h. The title compound from Preparative Example 59, Step C, (2.4g, 6.04mmoles) in anhydrous DMF (10mL) was added and the mixture was stirred at 25°C for 1h. The product was worked up as described in Preparative Example 2,
- 20 Step A and chromatographed on silica gel using 3% methanol in dichloromethane as the eluant to give the title mixture of compounds (1.584g, 85%) (4-Me:5-Me::58:42): CIMS: m/z 308.25 (MH⁺); 4-Me: δ_H (CDCl₃) 1.44 (9H, s, CH₃), 2.21 (3H, s, Im-4-Me), 3.82 (2H, m, CH₂-Im), 6.59 (1H, s, Im-H₉) and 7.33ppm (1H, s, Im-H₂);
- 25 δ_C (CDCl₃) CH₃: 13.8, 28.5, 28.5, 28.5; CH₂: 28.3, 32.1, 33.4, 33.4, 44.0, 47.1, 47.1; CH: 35.8, 115.2, 136.2; C: 79.3, 138.5, 154.9 and 5-Me: δ_H (CDCl₃) 1.44 (9H, s, CH₃), 2.19 (3H, s, Im-5-Me), 3.82 (2H, m, CH₂-Im), 6.77 (1H, s, Im-H₃) and 7.39ppm (1H, s, Im-H₂);
- δ_C (CDCl₃) CH₃: 9.3, 28.5, 28.5, 28.5; CH₂: 28.1, 32.1, 33.4, 33.4, 44.0, 44.0, 44.9; CH: 35.8, 127.0, 136.2; C: 79.3, 133.7, 154.9.
- 30

Step E

1N-tert-BUTOXYCARBONYL-4-[3-(1H-4-METHYLIMIDAZOL-1-
YL)PROPYL]PIPERIDINE



The mixture of compounds from Step D above (1.51g) was dissolved in anhydrous CH_2Cl_2 (10mL) at 0°C under argon. Trityl chloride (1.15g, 2 equivalents per equivalent of the 5-methyl isomer) was added and the mixture was stirred at 0°C for 2h. The reaction

10 mixture was introduced directly onto a silica gel column and the column was eluted with 50% ethyl acetate in acetone to give the pure 4-methyl isomer (0.635g, 65%): 4-Me: CIMS: m/z 308.30 (MH⁺); δ_{H} (CDCl_3) 1.44 (9H, s, CH_3), 2.22 (3H, s, Im-4-Me), 3.83 (2H, m, CH_2 -Im), 6.60 (1H, s, Im-H₅) and 7.33ppm (1H, s, Im-H₂);

15 δ_{C} (CDCl_3) CH_3 : 13.8, 28.5, 28.5, 28.5; CH_2 : 28.2, 32.0, 33.4, 33.4, 43.9, 47.1, 47.1; CH: 35.7, 115.2, 136.2; C: 79.3, 138.5, 154.8.

Step F

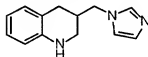
4-[3-(1H-4-METHYLIMIDAZOL-1-YL)PROPYL]PIPERIDINE



- 5 The title compound was deprotected as described in
 Preparative Example 57, Step D to give after chromatography on
 silica gel using 20% (10% conc. NH_4OH in methanol)-
 dichloromethane as the eluant, the title compound (0.3581g, 89%):
 CIMS: m/z 208.25 (MH^+); δ_{H} (CDCl_3) 2.12 (3H, s, Im-4-Me), 3.74 (2H,
 10 m, CH_2 -Im), 6.51 (1H, s, Im- H_3) and 7.25ppm (1H, s, Im- H_2);
 δ_{C} (CDCl_3) CH_3 : 13.6; CH_2 : 28.1, 33.3, 33.3, 33.9, 46.5, 46.5, 47.1;
 CH: 35.8, 115.1, 136.0; C: 138.2.

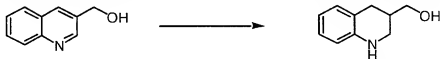
PREPARATIVE EXAMPLE 60

- 15 3(R/S)-[(1H-IMIDAZOL-1-YL)METHYL]-1,2,3,4-
 TETRAHYDROQUINOLINE



Step A

3(R/S)-(HYDROXYMETHYL)-1,2,3,4-TETRAHYDRO-QUINOLINE

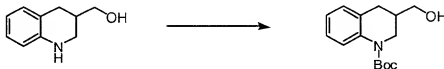


- 20 3-Hydroxymethylquinoline (0.45g, 2.83mmoles) (prepared as
 described in: B. R. Brown, D. Ll. Hammick and B. H. Thewlis, J.
 Chem. Soc., **1951**, 1145-1149.) was dissolved in methanol (100mL)
 and placed in a Parr bomb. Platinum (IV) oxide monohydrate
 25 (0.225g, 0.918mmoles) was added and the mixture was
 hydrogenated at 50psi at 25°C for 6h. The catalyst was removed by
 decantation and washed with methanol. The methanol was

evaporated to dryness and the product was chromatographed on silica gel using 3% (10% conc. NH_4OH in methanol)-dichloromethane as the eluant to give the title compound (0.3843g, 83%): CIMS: m/z 164.35 (MH^+); δ_{H} (CDCl_3) 6.50 (1H, d, Ar- H_{a}), 6.64 (1H, t, Ar- H_{b}), 6.98 (1H, d, Ar- H_{c}) and 6.99ppm (1H, m, Ar- H_{d}); δ_{C} (CDCl_3) CH_2 : 29.5, 44.0, 65.2; CH: 34.9, 114.2, 117.4, 126.9, 129.8; C: 120.2, 144.5.

Step B

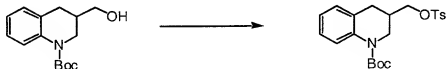
- 10 1N-tert-BUTOXYCARBONYL-3(R/S)-(HYDROXYMETHYL)-1,2,3,4-TETRAHYDROQUINOLINE



- The title compound from Step A above (2.578g, 15.79mmoles) was dissolved in THF (51.5mL) and sodium hydroxide (0.634g, 15.79mmoles) in water (51.5mL) was added. Di-tert-butyl dicarbonate (6.888g, 31.58mmoles) was added and the mixture was stirred at 25°C for 187h. Additional di-tert-butyl dicarbonate (0.6888g, 3.16mmoles) was added and the reaction was allowed to proceed for a total of 301h. The product was worked up and purified as described in Preparative Example 1, Step A to give the title compound (3.794g, 91%): FABMS; m/z 264.1 (MH^+); δ_{H} (CDCl_3) 1.50 (9H, s, CH_3), 7.03 (1H, m, Ar-H), 7.19-7.10 (2H, m, Ar-H) and 7.58ppm (1H, d, Ar-H); δ_{C} (CDCl_3) CH_3 : 28.3, 28.3, 28.3; CH_2 : 29.5, 45.1, 63.6; CH: 36.1, 124.0, 124.6, 125.6, 129.2; C: 81.5, 128.2, ~138.8, ~154.7.

Step C

1N-tert-BUTOXYCARBONYL-3(R/S)-[(4-TOSYLOXY)METHYL]-
1,2,3,4-TETRAHYDROQUINOLINE



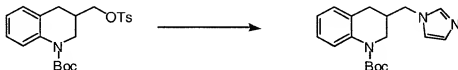
- 5 The title racemic compound from Step B above (0.322g, 1.22mmoles) was dissolved in anhydrous pyridine (2mL) and the solution was cooled to 0°C. 4-Toluenesulfonyl chloride (0.28g, 1.464mmoles) was added and the reaction was stirred at 0°C for 5h. The mixture was then heated at 40°C for 13h and worked up as described in Preparative Example 2, Step C to give the title compound (0.481g) which was used directly in Step E below.
- 10

The individual pure enantiomers from Step C above may be similarly treated to give the 3(R) and 3(S) enantiomers of the title compound.

15

Step D

1N-tert-BUTOXYCARBONYL-3(R/S)-[(1H-IMIDAZOL-1-YL)METHYL]-
1,2,3,4-TETRAHYDROQUINOLINE



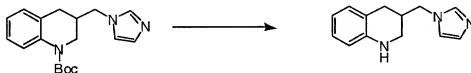
- 20 The title racemic product from Step D above was dissolved in anhydrous DMF (5mL) and sodium imidazole (0.1652g, 1.83mmoles) was added. The mixture was heated at 65°C under argon for 4h. The solution was evaporated to dryness and the residue was taken up in dichloromethane, washed with water, dried (MgSO₄), filtered and evaporated to dryness. Chromatography on silica gel using 2.5% (10% conc. NH₄OH in methanol)-dichloromethane afforded the title compound (0.3284g, 86%); ESMS: m/z 314.1 (MH⁺); δ_H (CDCl₃) 1.51 (9H, s, CH₃), 6.97 (1H, s, Im-H₂), 7.01 (1H, t, Ar-H₆), 7.06 (1H, t, Ar-H₇), 7.12 (1H, s, Im-H₄),
- 25

- 130 -
 7.17 (1H, t, Ar-H_g), 7.51 (1H, s, Im-H₂) and 7.68ppm (1H, d, Ar-H_g);
 δ_c (CDCl₃) CH₃: 28.4, 28.4, 28.4; CH₂: 31.0, 46.7, 49.5; CH: 35.9,
 119.1, 123.8/123.9, 126.4, 126.9, 129.0, 129.8, 137.5; C: 81.5,
 137.5, 138.2, 153.7.

- 5 The individual pure enantiomers from Step D above may be similarly treated to give the 3(R) and 3(S) enantiomers of the title compound.

Step E

- 10 3(R/S)-[(1H-IMIDAZOL-1-YL)METHYL]-1,2,3,4-TETRAHYDROQUINOLINE



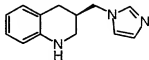
- The title racemic compound from Step E above (0.3208g, 1.024mmoles) was dissolved in anhydrous methanol (5.42mL) and 10% conc. H₂SO₄ / dioxane (v/v) (13.95mL) was added and the mixture was stirred at 25°C for 1h. The product was worked up as described in Preparative Example 1, Step D above. Chromatography on silica gel using 2.5% (10% conc. NH₄OH in methanol)-dichloromethane as the eluant gave the title compound (0.19g, 20 90%): CIMS: m/z 214.2 (MH⁺); δ_H (CDCl₃) 3.97 (2H, m, Im-CH₂), 6.51 (1H, d, Ar-H_g), 6.65 (1H, t, Ar-H_g), 6.95 (1H, s, Im-H₂), 6.96 (1H, t, Ar-H_g), 7.01 (1H, t, Ar-H_g), 7.09 (1H, s, Im-H₂) and 7.50ppm (1H, s, Im-H₂); δ_c (CDCl₃) CH₂: 30.2, 43.5, 49.0; CH: 33.7, 114.2, 117.7, 119.3, 127.3, 129.5, 130.0, 137.7; C: 118.4, 143.9.

Step F

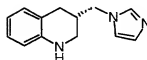
3(R)-[(1H-IMIDAZOL-1-YL)METHYL]-1,2,3,4-
TETRAHYDROQUINOLINE

and

5 3(S)-[(1H-IMIDAZOL-1-YL)METHYL]-1,2,3,4-TETRAHYDROQUINOLINE



3R



3S

The racemic title compound (0.6545g) from Step E above was separated by preparative HPLC on a Chiralpak® AD column

10 (50X5cm) using hexane-*iso*-propanol-diethylamine::80:20:0.2 as the eluant to give a less polar (-)-enantiomer (0.3244g): CIMS: m/z

214.15 (MH⁺); δ_H (CDCl₃) 3.97 (2H, m, Im-CH₂), 6.52 (1H, d, Ar-H₈), 6.68 (1H, t, Ar-H₆), 6.96 (1H, s, Im-H₅), 6.96 (1H, t, Ar-H₇), 7.02 (1H, t, Ar-H₉), 7.10 (1H, s, Im-H₄) and 7.49ppm (1H, s, Im-H₂); δ_C (CDCl₃)

15 CH₂: 30.2, 43.5, 49.0; CH: 33.7, 114.2, 117.7, 119.3, 127.3, 129.6, 130.0, 137.7; C: 118.5, 143.9; [α]_D^{20°C} -57.3° (c=10.43mg/2mL,

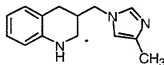
methanol) and a more polar (+)-enantiomer (0.3286g): CIMS: m/z 214.15 (MH⁺); δ_H (CDCl₃) 3.97 (2H, m, Im-CH₂), 6.52 (1H, d, Ar-H₈), 6.67 (1H, t, Ar-H₆), 6.96 (1H, s, Im-H₅), 6.96 (1H, t, Ar-H₇), 7.01 (1H,

20 t, Ar-H₉), 7.11 (1H, s, Im-H₄) and 7.50ppm (1H, s, Im-H₂); δ_C (CDCl₃) CH₂: 30.2, 43.5, 49.0; CH: 33.7, 114.2, 117.7, 119.3, 127.3, 129.6,

130.1, 137.7; C: 118.5, 143.9; [α]_D^{20°C} +56.8° (c=10.70mg/2mL, methanol), corresponding to the title compounds.

PREPARATIVE EXAMPLE 61

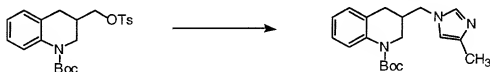
3-[(1H-4-METHYLIMIDAZOL-1-YL)METHYL]-1,2,3,4-
TETRAHYDROQUINOLINE



Step A

1002221-122001

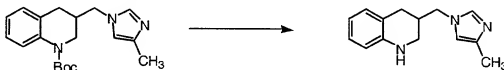
- 132 -
1N-tert-BUTOXYCARBONYL-3-[(1H-4-METHYLIMIDAZOL-1-
YL)METHYL]-1,2,3,4-TETRAHYDROQUINOLINE



- 4-Methylimidazole (0.9504g, 11.6mmoles) was dissolved in
5 anhydrous DMF (52mL) and 95% sodium hydride (0.2924g,
11.6mmoles) was added in portions to the stirred solution at 25°C
under argon. The mixture was stirred for 1h. The title racemic
compound from Preparative Example 60, Step C (4.394g,
10.5mmoles) in anhydrous DMF (25mL) was added and the mixture
10 was stirred at 25°C for 1h and then at 55-60°C for 7h. The mixture
was evaporated to dryness and the residue was chromatographed
on silica gel using 0.5%-2%-4%-6%-10% (10% conc. NH_4OH in
methanol)-dichloromethane as the eluant to give the racemic title
compound (1.93g, 56%) (4-Me:5-Me::1.46:1.0): CIMS: m/z 328.25
15 (MH^+); δ_{H} (CDCl_3) 1.51 (9H, s, CH_3), 2.20/2.24 (3H, s, 5-Me/4-Me),
3.81/3.88 (2H, m, 5-Me-Im- CH_2 /4-Me-Im- CH_2), 6.65/6.83 (1H, s, 4-
Me-Im- H_b /5-Me-Im- H_d), 6.99-7.07 (2H, m, Ar- H_f and Ar- H_g),
7.17/7.20 (1H, d, Ar- H_g), 7.36/7.43 (1H, s, 4-Me-Im- H_c /5-Me-Im- H_e)
and 7.67/7.71ppm (1H, d, Ar- H_f); δ_{C} (CDCl_3) 4-Me: CH_3 : 13.8, 28.4,
20 28.4, 28.4; CH_2 : 31.0, 46.8, 49.4; CH: 35.8, 115.6, 123.8, 123.9,
126.3, 129.1, 136.7; C: 81.4, 127.0, 138.2, 153.7; and 5-Me: CH_3 :
9.4, 28.4, 28.4, 28.4; CH_2 : 31.0, 46.9, 47.1; CH: 35.3, 123.9, 123.9,
126.4, 126.9, 129.1, 137.3; C: 81.5, 127.3, 138.9, 153.7.

25 Step B

3-[(1H-4-METHYLIMIDAZOL-1-YL)METHYL]-1,2,3,4-
TETRAHYDROQUINOLINE

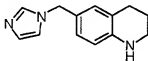


The title compound from Step A above was deprotected essentially as described in Preparative Example 57, Step D above and chromatographed on silica gel to give the title compound.

5

PREPARATIVE EXAMPLE 62

6-[(1H-IMIDAZOL-1-YL)METHYL]-1,2,3,4-TETRAHYDROQUINOLINE

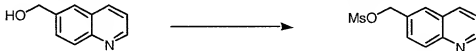


ROUTE 1

Step A

10

6-(METHANESULFONYLOXYMETHYL)QUINOLINE



6-Hydroxymethylquinoline (0.4325g, 2.72mmoles) (prepared by the method of: C. E. Kaslow and W. R. Clark, J. Org. Chem., **1953**, 18, 55-58.) and triethylamine (1.5147mL, 10.87mmoles)

15

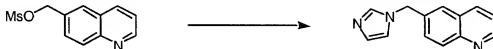
were dissolved in anhydrous dichloromethane (16mL) and the mixture was cooled to 0°C. Methanesulfonyl chloride (0.421mL, 5.43mmoles) was added and the mixture was stirred under argon at 0°C for 1h. Additional triethylamine (0.758mL, 5.435mmoles) and methanesulfonyl chloride (0.211mL, 2.72mmoles) were added and the reaction was allowed to proceed for a further 1h at 0°C. The mixture was evaporated to dryness to give the title compound which was used without further purification in the next step.

20

Step B

25

6-[(1H-IMIDAZOL-1-YL)METHYL]QUINOLINE

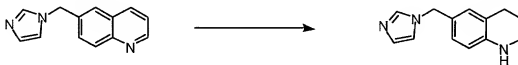


The title product from Step A above was dissolved in anhydrous DMF (10mL) and sodium imidazole (0.367g, 4.08mmoles) was added. The mixture was heated at 70°C under

argon for 2h and then evaporated to dryness. The product was chromatographed on silica gel to give the title compound (0.1559g, 27%): FABMS: m/z 210.0 (MH^+); δ_H ($CDCl_3$) 5.34 (1H, s, CH_2), 6.97 (1H, s, Im- H_9), 7.15 (1H, s, Im- H_4), 7.44 (1H, dd, Ar- H_3), 7.52 (2H, m, Ar- H_6 and Ar- H_7), 7.64 (1H, s, Im- H_2), 8.12 (2H, d, Ar- H_4 and Ar- H_5) and 8.95ppm (1H, d, Ar- H_2); δ_C ($CDCl_3$) CH_2 : 50.6; CH: 119.4, 121.8, 125.9, 128.4, 130.1, 130.5, 136.0, 137.6, 151.0; C: 128.2, 134.6, 147.9.

10 Step C

6-[(1H-IMIDAZOL-1-YL)METHYL]-1,2,3,4-TETRAHYDROQUINOLINE



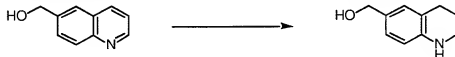
The title compound from Step B above (0.045g, 0.215mmoles) and methanol (11mL) were placed in a Parr bomb and platinum (IV) oxide monohydrate (0.05g, 0.204mmoles) was added. The mixture was hydrogenated at 50psi at 25°C for 2h. The catalyst was removed by decantation and washed with methanol. The methanol was evaporated to dryness and the product was chromatographed on silica gel using 3% (10% conc. NH_4OH in methanol)-

20 dichloromethane as the eluant to give the title compound (0.0325g, 71%): CIMS: m/z 214.15 (MH^+); δ_H ($CDCl_3$) 1.92 (2H, t, 3- CH_2), 2.61 (2H, m, 4- CH_2), 3.30 (2H, m, 2- CH_2), 4.93 (2H, s, CH_2), 6.42 (1H, d, Ar- H_9), 6.77 (1H, s, Ar- H_2), 6.79 (1H, d, Ar- H_3), 6.90 (1H, bs, Im- H_9), 7.07 (1H, bs, Im- H_4) and 7.52ppm (1H, bs, Im- H_2); δ_C ($CDCl_3$) CH_2 : 21.9, 27.0, 41.9, 50.8; CH: 114.2, 119.2(b), 126.4, 128.7, 129.1, 137.2(b); C: 121.6, 123.8, 144.8.

ROUTE 2

Step A

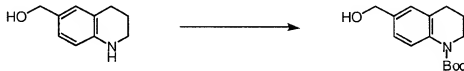
6-HYDROXYMETHYL-1,2,3,4-TETRAHYDROQUINOLINE



- 5 6-Hydroxymethylquinoline (1g, 6.28mmoles) (prepared by the method of: C. E. Kaslow and W. R. Clark, J. Org. Chem., **1953**, 18, 55-58.) and methanol (200mL) were placed in a Parr bomb and platinum (IV) oxide monohydrate (0.5g, 2.04mmoles) was added. The mixture was hydrogenated at 50psi at 25°C for 2h. The catalyst
- 10 was filtered off and washed with methanol. The combined filtrates were evaporated to dryness and the product was chromatographed on silica gel using 1.5% (10% conc. NH₄OH in methanol)-dichloromethane as the eluant to give the title compound (0.7044g, 68%): CIMS: m/z 164.35 (MH⁺); δ_H (CDCl₃) 1.93 (2H, m, 3-CH₂) and
- 15 2.76 (2H, t, 4-CH₂), 3.30 (2H, m, 2-CH₂), 4.50 (2H, s, CH₂OH), 6.45 (1H, d, Ar-H₅), 6.96ppm (2H, m, Ar-H₆ and Ar-H₇); δ_C (CDCl₃) CH₂: 22.1, 27.0, 42.0, 65.6; CH: 114.2, 126.4, 129.2; C: 121.5, 129.4, 144.5.

20 Step B

1N-tert-BUTOXYCARBONYL-6-HYDROXYMETHYL-1,2,3,4-TETRAHYDROQUINOLINE



- 25 The title compound from Step A above (0.684g, 4.19mmoles) was dissolved in THF (25mL) and sodium hydroxide 0.21g, 5.25mmoles) in water (10mL) was added. Di-tert-butyl dicarbonate (1.26g, 5.76mmoles) was added and the mixture was stirred at 25°C for 92h. Additional di-tert-butyl dicarbonate (0.628g, 2.88mmoles) was added and the reaction was continued for a total of 116h. The
- 30 reaction was worked up as described in Preparative Example 1 Step

A above and the product was chromatographed on silica gel using 0.5% (10% conc. NH_4OH in methanol)-dichloromethane as the eluant to give the title compound (0.7978g, 72%); ESMS: m/z 264.1 (MH^+); δ_{H} (CDCl_3) 1.52 (9H, s, CH_3), 1.91 (2H, m, 3- CH_2), 2.76 (2H, t, 4- CH_2), 3.70 (2H, m, 2- CH_2), 4.60 (2H, s, CH_2OH), 7.09 (1H, s, Ar- H), 7.12 (1H, d, Ar- H) and 7.64ppm (1H, d, Ar- H); δ_{C} (CDCl_3) CH_3 : 28.4, 28.4, 28.4; CH_2 : 23.5, 27.6, 44.7, 65.1; CH: 124.3, 124.7, 127.4; C: 80.9, 130.1, 135.6, ~138.4, ~154.2.

10 Step C

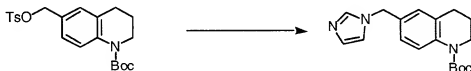
1N-tert-BUTOXYCARBONYL-6-(4-TOSYLOXYMETHYL)-1,2,3,4-TETRAHYDROQUINOLINE



The title compound from Step B above may be reacted with 4-toluenesulfonyl chloride and pyridine under essentially the same conditions as described in Preparative Example 58, Step C and chromatographed on silica gel to give the title compound.

20 Step D

1N-tert-BUTOXYCARBONYL-6-[(1H-IMIDAZOL-1-YL)METHYL]-1,2,3,4-TETRAHYDROQUINOLINE



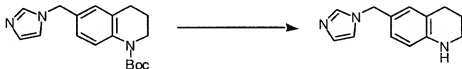
The title compound from Step C above may be reacted with sodium imidazole in anhydrous DMF under essentially the same conditions as described in Preparative Example 62, Route 1, Step B and chromatographed on silica gel to give the title compound.



- The title compound from Route 2, Step B above (0.5166g, 1.96mmoles) was dissolved in anhydrous THF (5.5mL) and N,N'-carbonyldiimidazole (0.668g, 4.12mmoles) was added and the mixture was heated under reflux at 75°C for 4.5h. The solution was evaporated to dryness and chromatographed on silica gel using 2% (10% conc. NH₄OH in methanol)-dichloromethane as the eluant to give the title compound (0.0612g, 10%): CIMS: m/z 314.25 (MH⁺); δ_{H} (CDCl₃) 1.51 (9H, s, CH₃), 1.92 (2H, m, 3-CH₂), 2.72 (2H, d, 4-CH₂), 3.69 (2H, d, 2-CH₂), 5.04 (2H, s, CH₂-Im), 6.85 (1H, s, Im-H₂), 6.91 (1H, s, Ar-H₉), 6.97 (1H, d, Ar-H₉), 7.08 (1H, s, Im-H₂), 7.59 (1H, s, Im-H₂) and 7.67ppm (1H, d, Ar-H₃); δ_{C} (CDCl₃) CH₃: 28.4, 28.4, 28.4; CH₂: 23.4, 27.6, 44.8, 50.5; CH: 119.4, 124.5, 125.0, 127.6, 129.4, 137.3; C: 81.1, 130.5, 130.5, 138.7, 153.9.

Step E

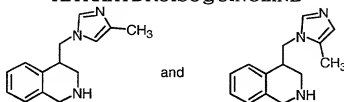
6-[(1H-IMIDAZOL-1-YL)METHYL]-1,2,3,4-TETRAHYDROQUINOLINE



- The title compound from Step D above may be deprotected essentially as described in Preparative Example 57, Step D and chromatographed on silica gel to give the title compound.

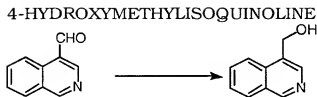
PREPARATIVE EXAMPLE 63

- 4(R/S)-[(1H-4/5METHYLIMIDAZOL-1-YL)METHYL]-1,2,3,4-TETRAHYDROISOQUINOLINE



ROUTE 1

Step A

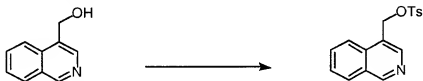


- 5 4-Isoquinolinecarboxaldehyde (6.15g, 39.13mmoles) (prepared by the method of: J. B. Wommack, T. G. Barbee, Jr., D. J. Thoennes, M. A. McDonald and D. E. Pearson, J. Heterocyclic Chem., 1969, 6, 243-245.) was dissolved in anhydrous dichloromethane (369mL) and the solution was cooled to 0°C.
- 10 Borane-dimethyl sulfide complex (1M in THF) (5.23mL, 5.09mmoles) (as described in: E. Mincione, J. Org. Chem., 1978, 43, 1829-1830) was added and the mixture was stirred at 0°C for a 1.5h. Additional borane-dimethylsulfide complex (1M in THF) (10.455mL, 1.35mmoles) was added and the reaction was stirred for an
- 15 additional 2h at 0°C. Methanol (93.3mL) was added and the solution was evaporated to dryness and chromatographed on silica gel using 2-3% (10% conc. NH₄OH in methanol)-dichloromethane as the eluant to give unreacted 4-Isoquinolinecarboxaldehyde (~23%), 4(1,2-dihydroisoquinoline)carboxaldehyde (identical to that
- 20 described in Preparative Example 63, Route 3, Step A (~27%) and the title compound (1.94g, 31%).

Alternatively the title compound may be prepared by catalytic hydrogenation of 4-isoquinolinecarboxaldehyde using 10% Pd-Al₂O₃ as the catalyst (as described in: J. Vassant, G. Smets, J. P. Declercq, G. Germain and M. Van Meerssche, J. Org. Chem., 1980, 45, 1557-1565).

Step B

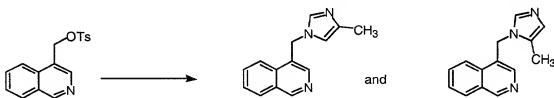
4-[(4-TOLUENESULFONYLOXY)METHYL]ISOQUINOLINE



- To a stirred solution of the title compound from Step A above
- 5 (1.94g, 12.2mmoles) in anhydrous pyridine (14mL) at 0°C was added 4-toluenesulfonyl chloride (2.784g, 14.6mmoles) and the mixture was stirred at 0°C for 2.5h. The solution was evaporated to dryness and the product was azeotroped with toluene and then taken up in dichloromethane and washed with saturated aqueous
- 10 sodium bicarbonate, filtered and evaporated to give the title compound which was used without purification in the next step.

Step C

4-[(1H-4/5-METHYLIMIDAZOL-1-YL)METHYL]ISOQUINOLINE

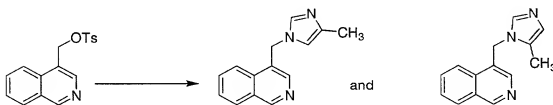


- 15 4-Methylimidazole (1.099g, 13.38mmoles) was dissolved in anhydrous DMF (33.5mL) and 95% sodium hydride (0.338g, 13.42mmoles) was added in portions to the stirred solution at 25°C. The title compound from Step B above was dissolved in anhydrous
- 20 DMF (14mL) and added dropwise to the stirred solution at 25°C over 20min. The mixture was stirred at 25°C for 17h and evaporated to dryness. The residue was taken up in dichloromethane and washed with water, dried(MgSO₄), filtered and evaporated to dryness. The product was chromatographed on silica
- 25 gel using 2.5% methanol in dichloromethane as the eluant to give a mixture of the title compounds (0.5085g, 19%) (4-Me:5-Me::1.2:1):
- δ_{H} (CDCl₃) 2.18/2.22 (3H, s, 4-Me/5-Me), 5.46 (2H, s, CH₂-Im), 6.63/6.89 (1H, s, 4-Me: Im-H₃/5-Me: Im-H₄), 7.43/7.55 (1H, s, 5-

Me: Im-H₂/4-Me: Im-H₃, 7.63-7.86 (3H, d and t, Ar-H_{6,7,8}), 8.02/8.38 (1H, s, 5-Me: Ar-H₃/ 4-Me: Ar-H₃), 8.05 (0.5H, d, 5-Me: Ar-H₃) and 9.26/9.28ppm (1H, s, 5-Me: Ar-H₁/4-Me: Ar-H₁), δ_c (CDCl₃) 4-Me: CH₃: 13.6; CH₂: 46.5; CH: 115.7, 121.8, 127.8, 128.7, 131.6, 136.3, 143.3, 154.1; C: 124.7, 128.5, 133.8, 138.7; and 5-Me: CH₃: 9.5; CH₂: 44.4; CH: 121.6, 127.4, 127.8, 128.7, 131.5, 137.2, 142.0, 153.7; C: 124.8, 128.2, 133.4, 138.7.

Step D

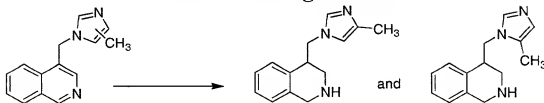
- 10 4-[(1H-4-METHYLIMIDAZOL-1-YL)METHYL]ISOQUINOLINE
and
4-[(1H-5-METHYLIMIDAZOL-1-YL)METHYL]ISOQUINOLINE



- 15 The title mixture of regio-isomers from Step C above (0.45g) was subjected to chiral HPLC on a Chiralpak® HPLC column using hexane:iso-propanol:diethylamine::85:15:09.2 to give first the 4-methyl isomer (0.0406g); FABMS: m/z 224.0 (MH⁺); δ_H (CDCl₃) 2.18 (3H, s, 4-CH₃), 5.46 (2H, s, CH₂-Im), 6.62 (1H, s, Im-H₂), 7.54 (1H, s, Im-H₂), 7.67 (1H, t, Ar-H₈), 7.76 (1H, t, Ar-H₇), 7.84 (1H, d, Ar-H₆), 8.04 (1H, d, Ar-H₆), 8.39 (1H, s, Ar-H₃) and 9.27ppm (1H, s, Ar-H₁); δ_c (CDCl₃) CH₃: 13.6; CH₂: 46.5; CH: 115.7, 121.8, 127.8, 128.7, 131.6, 136.3, 143.3, 154.1; C: 124.7, 128.7, 133.8, 138.8; and then the 5-methyl isomer (0.0361g); FABMS: m/z 224.1 (MH⁺); δ_H (CDCl₃) 2.20 (3H, s, 5-CH₃), 5.45 (2H, s, CH₂-Im), 6.86 (1H, s, Im-H₁), 7.41 (1H, s, Im-H₂), 7.68 (1H, t, Ar-H₈), 7.98 (1H, t, Ar-H₇), 7.84 (1H, d, Ar-H₆), 8.02 (1H, s, Ar-H₃), 8.05 (1H, d, Ar-H₆) and 9.22ppm (1H, s, Ar-H₁); δ_c (CDCl₃) CH₃: 9.4; CH₂: 44.3; CH: 121.5, 126.9, 127.9, 128.8, 131.7, 137.0, 141.7, 153.6; C: 124.9, 128.2, 133.4, 138.7
- 25 and an overlap fraction (0.28g).
- 30

Step E

4-[(1H-4/5-METHYLIMIDAZOL-1-YL)METHYL]-1,2,3,4-TETRAHYDROISOQUINOLINE



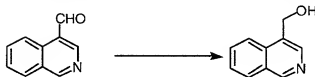
- 5 The title compound from Step C above (0.346g, 1.55mmoles) was dissolved in anhydrous methanol (80mL) and platinum (IV) oxide.monohydrate (0.11g) was added. The mixture was hydrogenated at 25°C at 50psi in a Parr bomb for 2h. The catalyst was filtered off and washed with methanol and the methanol
- 10 filtrates were evaporated to dryness. The residue was chromatographed on silica gel using 3% (10% conc. NH_4OH in methanol)-dichloromethane as the eluant to give the title 4-methyl compound (0.0299g, 9%): ESMS: m/z 228.0; δ_{H} (CDCl_3) 2.24 (3H, s, Im-4- CH_3), 2.81 (1H, bs, NH), 2.93 (2H, m, 3- CH_2), 3.03 (1H, m, 4-CH), 4.04 (2H, s, 1- CH_2), 4.08, 4.27 (2H, dd, CH_2 -Im), 6.68 (1H, Im- H_2), 7.01-7.09 (2H, m, Ar-H), 7.18 (2H, m, Ar-H) and 7.36ppm (1H, s, Im- H_3); δ_{C} (CDCl_3) CH_3 : 13.8; CH_2 : 45.0, 48.4, 51.1; CH: 39.6, 115.6, 126.5, 126.8, 126.9, 129.1, 136.9; C: 134.5, 135.7, 138.6, and the title 5-methyl compound (0.0641g, 18%): CH_3 : 9.3; CH_2 :
- 15 44.9, 48.8, 50.5; CH: 39.4, 126.5, 126.9, 126.9, 129.0, 136.7; C: 127.0, 134.4, 135.7, 138.5.
- 20

ROUTE 2

Step A

25

4-HYDROXYMETHYLISOQUINOLINE



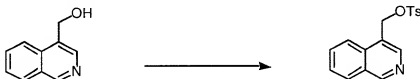
4-Isoquinolinecarboxaldehyde (1mmole) [prepared by the method of: J. B. Wommack, T. G. Barbee, Jr., D. J. Thoennes, M. A.

McDonald and D. E. Pearson, J. Heterocyclic Chem., **1969**, 6 , 243-245.) is dissolved in anhydrous THF (50mL) and treated with borane-methyl sulfide (0.3mmoles) (as described in: E. Mincione, J. Org. Chem., 1978, 43 , 1829-1830) at 0°C for 0.5-1h and worked up in the usual way to give the title compound.

Alternatively the title compound may be prepared by catalytic hydrogenation of 4-isoquinolinecarboxaldehyde using 10% Pd-Al₂O₃ as the catalyst (as described in: J. Vassant, G. Smets, J. P. Declercq, G. Germain and M. Van Meerssche, J. Org. Chem., **1980**, 45 , 1557-1565).

Step B

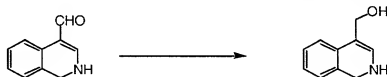
4-[[4-TOLUENESULFONYLOXY]METHYL]ISOQUINOLINE



The title compound from Step A above is dissolved in anhydrous pyridine and cooled to 0°C with stirring. 4-Toluenesulfonyl chloride is added and the reaction is carried out as described in Preparative Example 60, Step D to give the title compound which may be used without further purification.

Step C

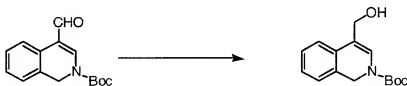
4-HYDROXYMETHYL-1,2-DIHYDROISOQUINOLINE



The title compound from Step A above may be selectively reduced with freshly prepared zinc borohydride (as described in: D. C. Sakar, A. R. Das and B. C. Ranu, J. Org. Chem., 1990, 55, 5799-5801.) to give title allylic alcohol.

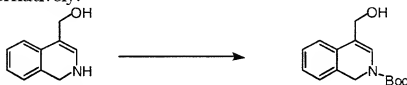
Step D

- 143 -
N-tert-BUTOXYCARBONYL-4-HYDROXYMETHYL-1,2-
DIHYDROISOQUINOLINE



- The title compound from Step B above is reacted with zinc
5 borohydride as described in Step C above to give the title
compound.

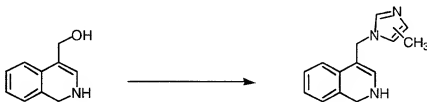
Alternatively:



- 10 The title compound from Step C above is reacted with di-tert-
butyldicarbonate and sodium hydroxide as described in Preparative
Example 57, Step A to give the title compound.

Step E

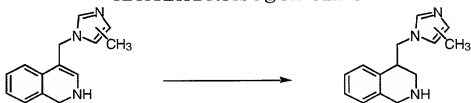
- 15 4(R/S)-[(1H-4/5-METHYLIMIDAZOL-1-YL)METHYL]-1,2-
DIHYDROISOQUINOLINE



- The title compound from Step C above may be reacted with
N,N'-carbonyldiimidazole using the procedure described in
20 Preparative Example 22, part two of Step D, to give the title
compounds.

Step F

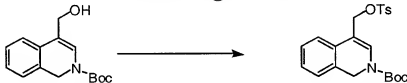
4(R/S)-[(1H-4/5-METHYLIMIDAZOL-1-YL)METHYL]-1,2,3,4-TETRAHYDROISOQUINOLINE



- 5 The title compounds of Step E above is reduced with platinum (IV) oxide as described in Route 1, Step D above to give the title compounds.

Step G

10 4[4-(TOLUENESULFONYLOXY)METHYL]-1,2-DIHYDROISOQUINOLINE



- 15 The title compound from Step D above is reacted with 4-toluenesulfonyl chloride in pyridine as described in Preparative Example 4, Step D to give the title compound.

Step H

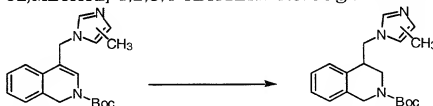
2N-tert-BUTOXYCARBONYL-4(R/S)-[(1H-4/5-METHYLIMIDAZOL-1-YL)METHYL]-1,2-DIHYDROISOQUINOLINE



- 20 The title compounds from Step G above was reacted with sodium 4-methylimidazole as described in Route 1, Step C above to give the title compounds.
- 25 The regio-isomers may be separated by chiral HPLC on a Chiralpak® column, or by treatment with trityl chloride as described above.

Step I

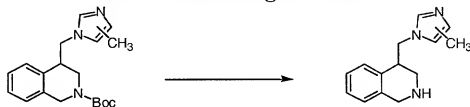
2N-tert-BUTOXYCARBONYL-4(R/S)-[(1H-4/5-METHYLIMIDAZOL-1-YL)METHYL]-1,2,3,4-TETRAHYDROISOQUINOLINE



- 5 The title compounds from Step H above were reduced with platinum (IV) oxide as described in Route 1 Step D above to give the title compounds.

Step J

- 10 4(R/S)-[(1H-4/5-METHYLIMIDAZOL-1-YL)METHYL]-1,2,3,4-TETRAHYDROISOQUINOLINE

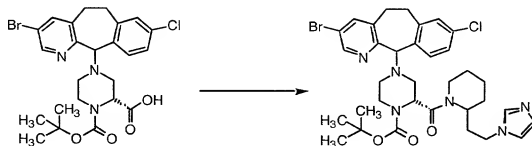


- 15 The title compounds from Step H above were deprotected as described in Preparative Example 57, Step D, to give the title compounds.

EXAMPLE 74

- 1,1-DIMETHYLETHYL-4-(3-BROMO-8-CHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YL)-2(R)-[[2-[2-(1H-IMIDAZOL-1-YL)ETHYL]-1-PIPERIDINYL]CARBONYL]-1-PIPERAZINECARBOXYLATE

Route 1

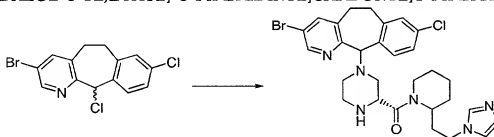


1,1-Dimethylethyl-4-(3-bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-2(R)-carboxy-1-piperazinecarboxylate (0.250g, 0.466mmoles) (prepared as described in Preparative Example 6), 2-[2-(1H-imidazol-1-yl)ethyl]piperidine (0.1085g, 0.6054mmoles) (prepared as described in Preparative Example 1), 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (0.116g, 0.6054mmoles), 1-hydroxybenzotriazole (0.0818g, 0.6054mmoles) and 4-methylmorpholine (0.0665mL, 0.6054mmoles) were dissolved in anhydrous DMF (10mL) and the mixture was stirred under argon at 25°C for 18h. The solution was evaporated to dryness and the residue was washed with water, dried (MgSO₄), filtered and evaporated to dryness. The residue was chromatographed silica gel using 1% (10% conc. NH₄OH in methanol)-dichloromethane as the eluant to give the title compound (0.0617g, 19%): ESMS: m/z 697.2 (MH⁺); δ_H (CDCl₃) 6.97 (1H, broad s, Im-H₃), 7.04 (1H, broad s, Im-H₄), 7.09-7.20 (broad m, Ar-H), 7.56 (2H, broad s, Ar-H and Im-H₂) and 8.38ppm (1H, broad s, Ar-H₂); δ_C (CDCl₃) CH₃: 28.4, 28.4, 28.4; CH₂: 18.9/19.1, 25.2/25.3/25.8, 30.4, 30.5, 31.4/31.6, 36.6, 40.2, 42.9, 43.4/43.7, 50.3, 52.7/53.0; CH: 45.8/46.4, 50.1/51.7/52.2, 78.3/78.4/~79.3, ~119.0, 126.3, ~129.8, 130.7/130.8, 132.5/132.6, ~137.1, 141.4/141.5, 146.9; C: 80.4, 120.0, 134.3, 134.8, 137.5, 141.0, 155.9, 156.8, 157.2.

25 Route 2

Step A.

4-(3-BROMO-8-CHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YL)-2(R)-[[2-[2-(1H-IMIDAZOL-1-YL)ETHYL]-1-PIPERIDINYL]CARBONYL]-1-PIPERAZINE

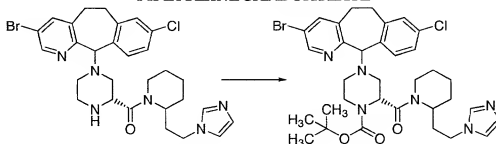


3-Bromo-8,11-dichloro-6,11-dihydro-5H-

benzo[5,6]cyclohepta[1,2-b]pyridine (prepared as described in Preparative Example 40 (U.S. 5,719,148) was reacted with the title compound from Preparative Example 1, Step B, and triethylamine, in a mixture of anhydrous THF and dichloromethane at 25°C to give the title compound.

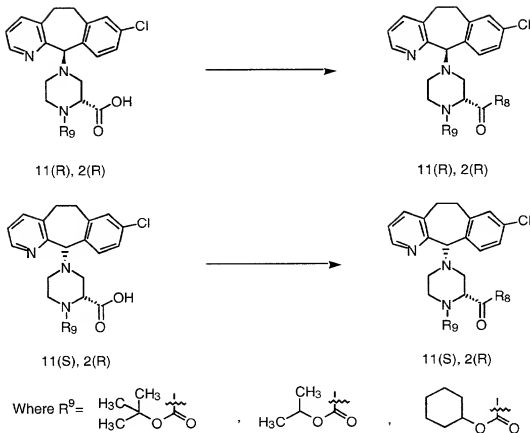
Step B

1,1-DIMETHYLETHYL 4-(3-BROMO-8-CHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YL)-2(R)-[[2-[2-[(1H-IMIDAZOL-1-YL)ETHYL]-1-PIPERIDINYL]CARBONYL]-1-PIPERAZINECARBOXYLATE



The title compound from Example 74, Step A was reacted with di-tert-butyl dicarbonate and sodium hydroxide in THF-water (1:1) at 25°C as described in Preparative Example 57, Step A, and the product was chromatographed on silica gel, to give the title compound.

- 148 -
EXAMPLES 75-86

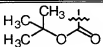
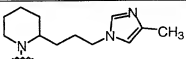
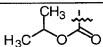
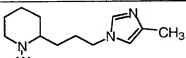
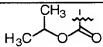
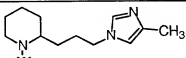

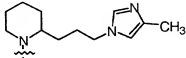

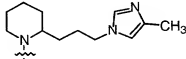
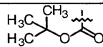
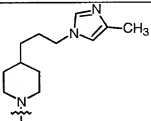


Using essentially the same procedure as described in Example 74 above the 11(R),2(R) and 11(S),2(R) acids from
 5 Preparative Example 30, may be reacted with the product from Preparative Example 58, Step E to give the targets of Examples 75-80; or with the product from Preparative Example 59, Step E to give the targets of Examples 81-86, respectively (Table 11).

TABLE 11

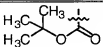
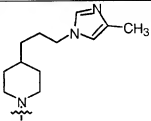
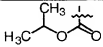
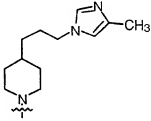
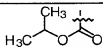
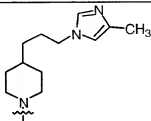
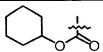
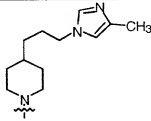
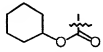
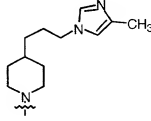
Ex	Product	
	R^6	R^6
75	<p>11(R), 2(R)</p>	<p>2(R/S)</p>

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TABLE 11 - continued

Ex	Product	
	R ⁹	R ⁸
76	 11(S),2(R)	 2(R/S)
77	 11(R),2(R)	 2(R/S)
78	 11(S),2(R)	 2(R/S)
79	 11(R),2(R)	 2(R/S)
80	 11(S),2(R)	 2(R/S)
81	 11(R),2(R)	 4(R/S)

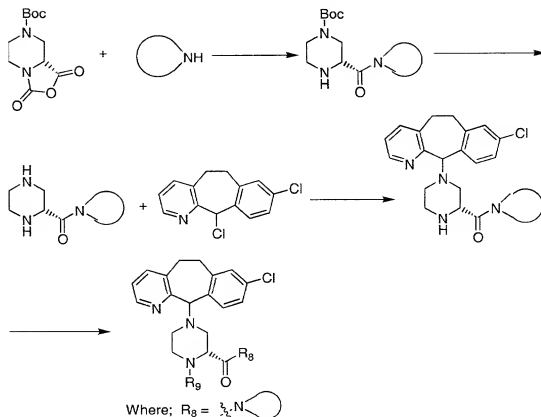
10028251.12004

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TABLE 11 - continued

Ex	Product	
	R ³	R ⁶
82	 11(S),2(R)	 4(R/S)
83	 11(R),2(R)	 4(R/S)
84	 11(S),2(R)	 4(R/S)
85	 11(R),2(R)	 4(R/S)
86	 11(S),2(R)	 4(R/S)


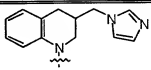

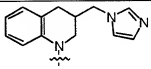

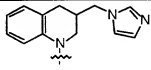

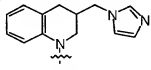

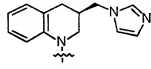

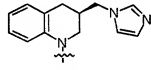

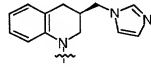

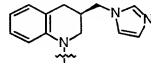
100221-1528201

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EXAMPLE 87-110



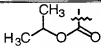
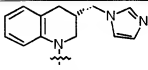
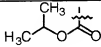
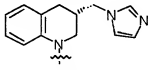

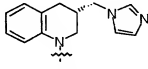

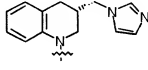
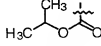
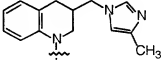
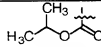
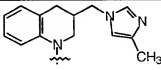

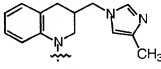

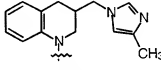
- By reacting the anhydride from Preparative Example 3 as shown in the scheme above, with the product of Preparative
- 5 Example 60, Steps E, or F, one may obtain the intermediate of Examples 87-98; or with the product of Preparative Example 61, Step B, one may obtain the intermediate of Examples 99-102; or with the product of Preparative Example 62, Step C, one may obtain the intermediate of Examples 103-106; or with the intermediate of
- 10 Preparative Example 63, Step D of Route 1, or Steps F or J of Route 2 one may obtain the intermediate of Examples 107-110. By reacting the intermediates so obtained with 8,11-dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (prepared as described in US 5,807,853, Sept. 15, 1998) one may obtain, after
- 15 reaction with either di-tert-butylidycarbonate and sodium hydroxide, or with *iso*-propyl chloroformate and triethylamine, or with cyclohexyl chloroformate and triethylamine as described herein, the title compounds of Examples 87-110 (Table 12).

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TABLE 12

Ex	Product	
	R ⁹	R ⁸
87	 11(R),2(R)	 3(R/S)
88	 11(S),2(R)	 3(R/S)
89	 11(R),2(R)	 3(R/S)
90	 11(S),2(R)	 3(R/S)
91	 11(R),2(R)	 3(R)
92	 11(S),2(R)	 3(R)
93	 11(R),2(R)	 3(R)
94	 11(S),2(R)	 3(R)

10028251.12001

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TABLE 12 - continued

Ex	Product	
	R ³	R ⁸
95	 11(R),2(R)	 3(S)
96	 11(S),2(R)	 3(S)
97	 11(R),2(R)	 3(S)
98	 11(S),2(R)	 3(S)
99	 11(R),2(R)	 3(R/S)
100	 11(S),2(R)	 3(R/S)
101	 11(R),2(R)	 3(R/S)
102	 11(S),2(R)	 3(R/S)


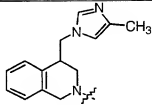
10029251.122001

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TABLE 12 - continued

Ex	Product	
	R ^a	R ^b
103	 11(R),2(R)	
104	 11(S),2(R)	
105	 11(R),2(R)	
106	 11(S),2(R)	
107	 11(R),2(R)	 4(R/S)
108	 11(S),2(R)	 4(R/S)
109	 11(R),2(R)	 4(R/S)

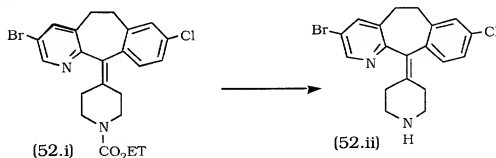
100221-1522001

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TABLE 12 - continued

Ex	Product	
	R ⁶	R ⁸
110	 11(S),2(R)	 4(R/S)

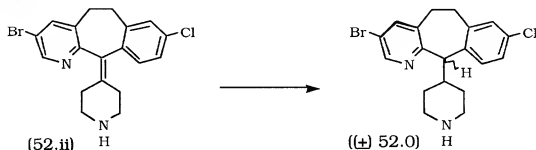
PREPARATIVE EXAMPLE 64

5 Step A



- A solution of 52.i (J. Med. Chem. 4890-4902 (1988))(205 g) in conc. HCl (1 L) and water (100 mL) is refluxed for 18h, then poured into ice (3 Kg). Aq. 50% NaOH is added to pH 12 followed by extraction with EtOAc (3x4 L), the extracts are washed with brine, dried and evaporated to afford 52.ii (166 g).

Step B



- 15 A 1M solution of DIBAL in toluene (908 mL) is added dropwise during 2h to a solution of 52.ii (166 g) in toluene (4 L) at rt. followed by stirring for 18 h. The mixture is cooled to 0-5°C and stirred for

1h and extracted with 1N HCl (2 L). The aqueous extract is basified to pH 10 with 50% NaOH and extracted with EtOAc (3x2 L). The extracts are evaporated and chromatographed on silica-gel (1 Kg). Elution with 10% MeOH/CH₂Cl₂ affords the title compound (+) 52.0

- 5 (104 g); HRMS (FAB) calcd for C₁₉H₂₁N₂⁷⁹BrCl 393.0556, found 393.0554.

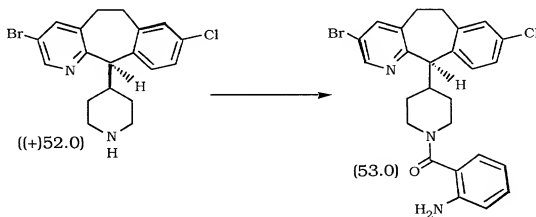
Step C

- 10 The racemate (+) 52.0 (96 g) is resolved by HPLC on a 8x30 cm CHIRALPAK AD column at 25°C with the UVdetector set at 290 nm. Elution with 0.05% diethylamine-methanol affords: Peak 1 (-) 52.0 (40 g); [α]_D²⁰ -28.4° (c 0.3, MeOH); Further elution with the same solvent affords: Peak 2 (+) 52.0 (42 g); [α]_D²⁰ +27.5° (c 0.3, MeOH).

15

PREPARATIVE EXAMPLE 65

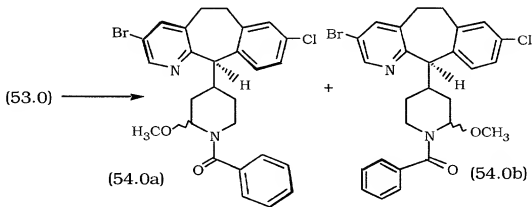
Step A



- 20 A solution of (+)-52.0 (2.3 g) in dimethylformamide (30 ml) is reacted with isatoic anhydride (1.25 g) in the presence of DMAP (0.1 g) at r.t. for 3hrs and is then evaporated under reduced pressure and residual dimethylformamide is azeotroped with toluene. The residue is dissolved in ethylacetate (50 ml) and the solution is extracted with 10% sodium carbonate (3x100 ml). The organic layer
- 25 is filtered through silica-gel (100ml) followed by elution with ethylacetate. The filtrate is evaporated under reduced pressure to

afford the title compound 53.0 as an amorphous solid (3.68 g).
MS(FAB): m/z 510 (MH)⁺.

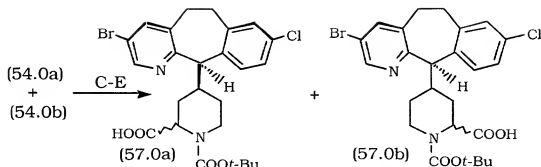
Step B



5

A solution of 53.0 (3.1 g) and sodium nitrite (0.8 g) in methanol (500 ml) is stirred at r.t. under nitrogen with cuprous chloride (0.15 g) while adding dropwise over 10 minutes a 4M hydrochloric acid/dioxane solution (3.9 ml). The reaction mixture is stirred for 24hrs followed by the addition of 10% sodium carbonate to pH 8, concentrated under reduced pressure, diluted with water (200 ml) and extracted with dichloromethane (4x100ml). The combined extract is evaporated under reduced pressure and the crude reaction product is flash chromatographed on silica-gel (400 ml). Elution with 25% ethylacetate-hexane affords after evaporation the title compound 54.0a and 54.0b as an off-white amorphous solid (2.97 g). ¹H NMR (CDCl₃, 300 MHz) δ 3.30 (s, 3H); MS (FAB) m/e 525 (MH)⁺.

Steps C-E



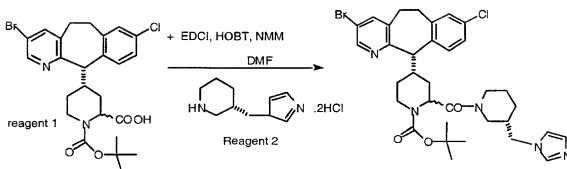
A solution of 54.0a and 54.0b (17 g) in methanol (150 ml) and 2N hydrochloric acid (170 ml) and conc. HCl (60 ml) is heated under reflux for 17 hrs, followed by evaporation under reduced pressure. The resulting amorphous solid is dissolved in methanol (160 ml) and sodium cyanide (15 g) is added with stirring until the reaction is basic (pH 8). The reaction is stirred for 2 h, diluted with dichloromethane (300 ml) and filtered. The filtrate is evaporated and the residue is dissolved in conc HCl (150 ml) and the mixture is heated in an oil bath (120°C) for 4h and is then evaporated under reduced pressure. The residue is dissolved in THF (100 ml) and 10% NaOH (30 ml) is added to pH>8 followed by the dropwise addition of a solution of (BOC)₂O (9 g) in THF (50 ml) with vigorous stirring for 24 h. The solution is concentrated to a low volume, stirred with hexane (2x120 ml) and ice-water followed by acidification of the aqueous layer with citric acid and extraction with EtOAc. The crude product obtained by evaporating the extract is purified by flash chromatography to afford the mixture of 57.0a and 57.0b as light tan solid that appears as a single tlc spot (16 g). ¹H NMR (CDCl₃, 300 MHz) δ 1.40 (s, 9H); MS (FAB) m/z 535 (MH)⁺.

The single tlc spot is a mixture of four isomers.

Following the above procedure (Steps A-E), except using Compound (-)-52.0 (17 g), a mixture of 58.0a and 58.0b is obtained as a light solid that appears as a single tlc spot (17 g). MS(ES) m/z 535 (MH)⁺.

10028251.122004

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EXAMPLE 118



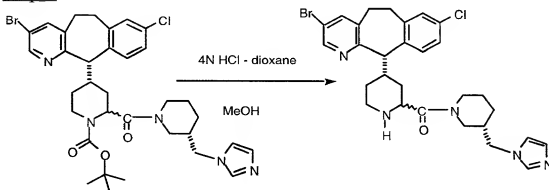
The imidazole (reagent 2), (220mg,0.92mmol) was added to a solution of the Boc-acid (reagent 1), (0.45g,0.842mmol), EDCI (200mg,1.043mmol),HOBT (130mg, 0.962mmol),and N-methylmorpholine (0.2ml,1.81mmol) in DMF (anhydrous, 3ml) at room temperature (20°C).The resultant solution was stirred overnight at 20°C.The solvent was evaporated, water (70ml) and EtOAc (120 ml) were added. The organic layer was separated,and washed with 10% Na₂CO₃ solution (50ml),then dried over MgSO₄, filtered and evaporated solvent yielding an oil, which chromatographed on silica gel eluting with 5% MeOH:MeCl₂ yielding the product as a white solid (425mg,74%). Mixture of 4 isomers A,B,C,D.

Mass Spec (ES,MH,682) High Resolution Mass Spec

Estimated(MH) 684.2139(Br =81) Observed 684.2120

EXAMPLE 119

Step A



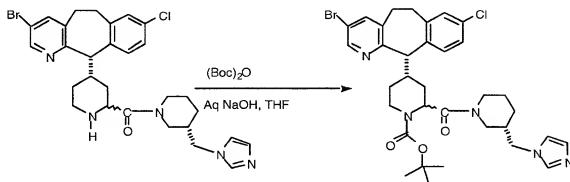
A solution of the tricyclic Isomers (A,B,C,D) from Example 118 (150mg,0.205mmol) in 4N HCl-dioxane (3ml) and MeOH(3ml) was stirred at 20°C for 3 hours. The solvent was evaporated,water (25ml)

and 10% NaOH (4ml) were added, then extracted with MeCl_2 (2x100ml). The organic layer was separated, dried over MgSO_4 , and solvent evaporated yielding a solid which was purified by chromatography on silica gel eluting with 3% $\text{MeOH}-\text{MeCl}_2$ containing 2% NH_4OH yielding the product as a white solid (70mg, 54% yield). Mixture of 2 Isomers (C,D) (PRODUCT 1) Mass Spec ES (MH) 582.

Further elution yielded a white solid (25mg, 20% yield).

Mixture of 2 isomers. (A,B) (PRODUCT 2) Mass Spec ES (MH) 582.

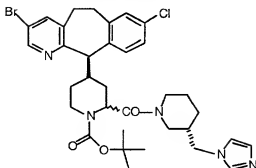
10 Step B



A solution of Boc dicarbonate (100mg, 0.45mmol) in THF (2ml) was added to a solution of the tricycle (170mg, 0.29mmol) (Isomers (C,D) Product 1 Step A in THF: H_2O (V/V 1:1) (10ml), and 10% NaOH (2ml) at 20°C. Then stirred at this temperature for 60 minutes. Water (5ml), and MeCl_2 (10ml) were added. The organic layer was separated, dried over MgSO_4 , filtered and solvent evaporated yielding an oil, which chromatographed on silica gel, eluting with 3% v/v $\text{MeOH}:\text{MeCl}_2$ yielding the product as a white solid (170mg) as a mixture of 2 isomers. Isomers C,D. Mass Spec (ES,MH) 682.

Following the above procedure but, substituting Product 2 from Step A (isomers A/B) for Product 1, the title Product 2 was obtained as a mixture of 2 isomers (A/B). Mass Spec (ES,MH) 682

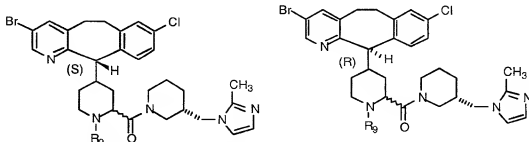
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EXAMPLE 120



Compounds with (R) stereochemistry at C₁₁ were obtained using the procedures of Examples 118 and 119, but substituting reagent 1, Example 118 with the corresponding (R) tricyclic isomer.

EXAMPLES 121-126

By substituting reagent 2, Example 118, with the corresponding 2-methyl imidazole analog, the following structures were obtained

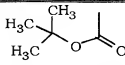
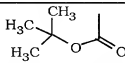
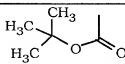
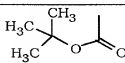
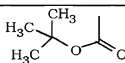


wherein R⁹ is defined in Table 14 below.

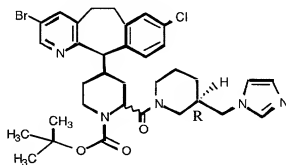
TABLE 14

Ex.	R ⁹	Isomer	C-11 Isomer
121	<p>MS ES (MH)=696</p>	A,B,C,D	S

- 162 -
TABLE 14 - continued

Ex.	R ⁹	Isomer	C-11 Isomer
122	 MS ES (MH)=696	A,B,C,D	R
123	 MS ES (MH)=696	C,D	S
124	 MS ES (MH)=696	A,B	S
125	 MS ES (MH)=696	C,D	R
126	 MS ES (MH)=696	A,B	

EXAMPLES 127-132



5

Following the procedures of Examples 118 and 119 the isomers identified in Table 15 below are obtained.

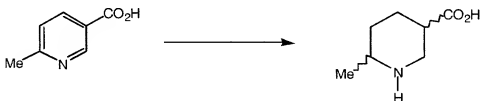
- 163 -
TABLE 15

Ex.	C-11 Isomer	Isomer	mass spectra observed (estimate)
127	R	A,B,C,D	684.2123 (684.2139)
128	R	A,B	684.2163 (684.2139)
129	R	C,D	684.2163 (684.2139)
130	S	A,B,C,D	684.2149 684.2139
131	S	A,B,	684.2139 (684.2139)

PREPARATIVE EXAMPLE 66

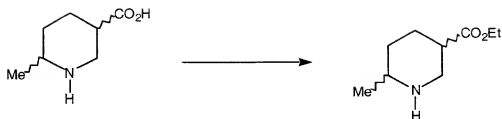
5

Step A



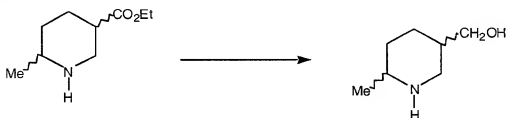
A solution of 6-methylnicotinic acid (9.97 g, 72.7 mmol),
water (100 mL) and ammonium hydroxide was hydrogenated (40
10 psi) in a Parr low-pressure hydrogenation apparatus with 5% Rh-
Al₂O₃ (3.22g) catalyst over 72 hours. The mixture was filtered and
the filtrate was concentrated *in vacuo* to give the title compound as
a white solid (10.58g, 100%, MH⁺ = 144).

Step B



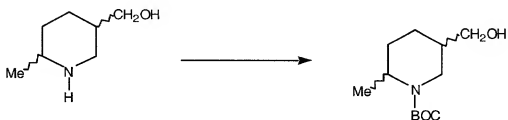
- A mixture of the title compound from Step A (10.40 g, 72.72 mmol), ethyl alcohol (190 proof, 50 ml) and HCl (4ml) was stirred at reflux for 4 hours. The reaction mixture was cooled to room temperature and poured into water. Basification of the mixture to pH=10 with 10% aqueous NaOH, extraction of the aqueous layer with EtOAc and drying of the organic phase over anhydrous Na_2SO_4 gave the title compound after filtration and concentration *in vacuo* (1.85 g, 15%, $\text{MH}^+ = 172$).

Step C



- Following the procedure set forth in Preparative Example 7 Step B but using the title compound from Preparative Example 66 Step B instead of the title compound from Preparative Example 7 Step A, the product was isolated as a mixture of diastereomers and used directly in Step D ($\text{MH}^+ = 130$).

Step D



- Following the procedure set forth in Preparative Example 7 Step C but using the title compound from Preparative Example 66

Step C instead of the title compound from Preparative Example 7
Step B, the product was isolated as a mixture of diastereomers (1.7
g, 70%, $MH^+ = 230$).

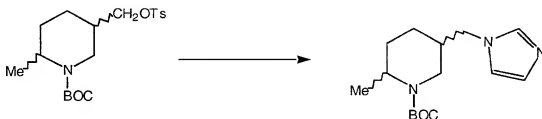
5 Step E



Following the procedure set forth in Preparative Example 7
Step D but using the title compound from Preparative Example 66
Step D instead of the title compound from Preparative Example 7

- 10 Step C, the product was isolated as a mixture of diastereomers and
used directly in Step F ($MH^+ = 384$).

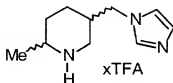
Step F



- 15 Following the procedure set forth in Preparative Example 7
Step E but using the title compound from Preparative Example 66
Step E instead of the title compound from Preparative Example 7
Step D, the product was isolated as a 5:1 mixture of diastereomers
(328 mg, 16 %, $MH^+ = 280$).

20

Step G



Following the procedure set forth in Preparative Example 7,
Step F, except using the title compound from Preparative Example

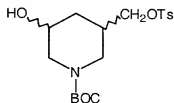
66, Step F instead of the title compound from Preparative Example 7, Step E, the amine hydrochloride was obtained (290 mg, 100%); $MH^+ = 180$.

5

PREPARATIVE EXAMPLE 67

Step A

If the procedures set forth in Preparative Example 66 Steps A-E were followed, except using 5-hydroxynicotinic acid instead of 6-methylnicotinic acid in Step A, the alcohol

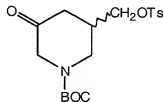


10

would be obtained.

Step B

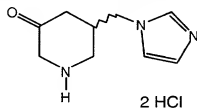
If the product from Step A were treated with PCC according to standard procedures set forth in the literature, then the ketone



would be obtained.

Step C

If the procedures set forth in Preparative Example 7 Steps E-F were followed, except using the title compound from Preparative Example 67 Step B instead of the title compound from Preparative Example 7 Step D in Step E, the amine hydrochloride

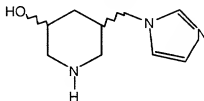


2 HCl

would be obtained.

Step D

- 5 If the product from Preparative Example 67 Step C were treated with excess NaBH_4 according to standard procedures set forth in the literature, then the alcohol

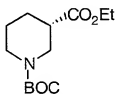


would be obtained.

10

PREPARATIVE EXAMPLE 68

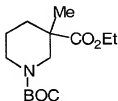
Step A



- Following the procedure set forth in Preparative Example 7 Step C, except using the title compound from Preparative Example 7, Step A instead of the title compound from Preparative Example 7, Step B the ester was obtained (62 g, 96%); $\text{MH}^+ = 258$.

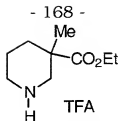
15

Step B



- 20 The product from Preparative Example 68, Step A was treated with LDA in anhydrous THF and the resulting anion was alkylated with methyl iodide to afford the title product (3.53 g, 82%); $\text{MH}^+ = 272$.

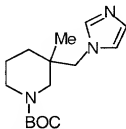
- 25 Step C



The title compound from Preparative Example 68, Step B was treated with TFA in CH_2Cl_2 to afford the amine as a TFA salt (1.63 g, 84%): $\text{MH}^+ = 172$.

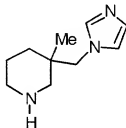
5

Step D



- Following the procedures set forth in Preparative Example 7, Steps B-E, except using the title compound from Preparative
- 10 Example 68, Step C instead of the title compound from Preparative Example 7, Step A in Step B, the imidazole product was obtained (0.445g, 100%): $\text{MH}^+ = 280$.

Step E

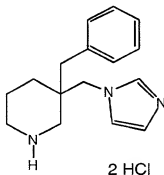


15

- Following the procedure set forth in Preparative Example 68 Step C, except using the title compound from Preparative Example 68 Step D, the amine was obtained as its TFA salt. The mixture
- 20 was basified with 1N NaOH and extracted with CH_2Cl_2 to afford the product (14.6 g, 96%): $\text{MH}^+ = 194$.

PREPARATIVE EXAMPLE 69

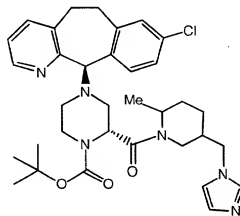
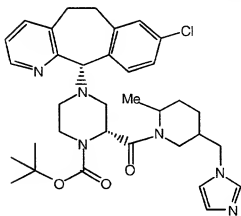
Following the procedures set forth in Preparative Example 68 Steps A-D, except using benzyl bromide in Preparative Example 68 Step B instead of methyl iodide, the amine hydrochloride



5

would be obtained.

EXAMPLE 133

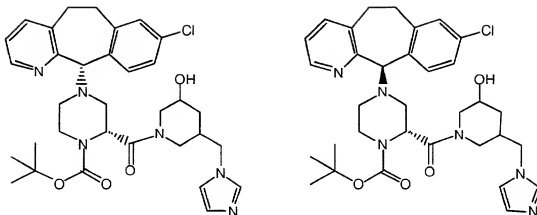


10

If the procedure set forth for preparing the compounds in Table 4 were followed using the title compound from Preparative Example 66 Step G, the 11(S) or 11(R) isomers of the carboxylic acid from Preparative Example 30, DEC, HOBT and NMM, the title products would be obtained.

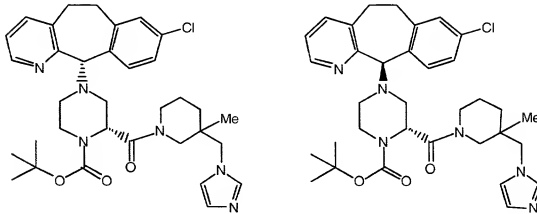
15

- 170 -
EXAMPLE 134



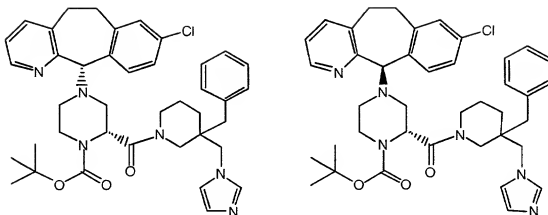
- If the procedure set forth for preparing the compounds in Table 4 were followed using the title compound from Preparative Example 67 Step D, the 11(S) or 11(R) isomers of the carboxylic acid from Preparative Example 30, DEC, HOBT and NMM, the title products would be obtained.

EXAMPLE 135



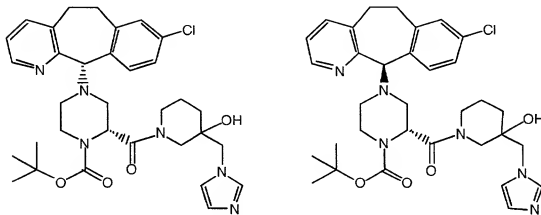
- If the procedure set forth for preparing the compounds in Table 4 were followed using the title compound from Preparative Example 68 Step D, the 11(S) or 11(R) isomers of the carboxylic acid from Preparative Example 30, DEC, HOBT and NMM, the title products would be obtained.

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EXAMPLE 136



- If the procedure set forth for preparing the compounds in Table 4 were followed using the title compound from Preparative Example 69, the 11(S) or 11(R) isomers of the carboxylic acid from Preparative Example 30, DEC, HOBT and NMM, the title products would be obtained.

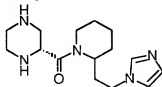
EXAMPLE 137



- If the procedure set forth for preparing the compounds in Table 4 were followed using the title compound from Preparative Example 70 Step B, the 11(S) or 11(R) isomers of the carboxylic acid from Preparative Example 30, DEC, HOBT and NMM, the title products would be obtained.

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PREPARATIVE EXAMPLE 71

2(R)-[[2-[2-(1H-IMIDAZOL-1-YL)ETHYL]-1-
PIPERIDINYL]CARBONYL]PIPERAZINE



5 Step A

BIS-(1,1-DIMETHYLETHYL) 2(R)-[[2-[2-(1H-IMIDAZOL-1-YL)ETHYL]-
1-PIPERIDINYL]CARBONYL]-1,4-PIPERAZINEDICARBOXYLATE

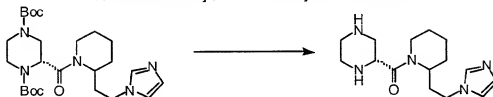


1,4-Di-N-tert-butoxycarbonylpiperazine-2(R)-carboxylate

- 10 (prepared as described in Preparative Example 2) (0.6946g, 2.1mmoles), 2(R/S)-[2-(1H-imidazol-1-yl)ethyl]piperidine (0.49g, 2.73mmoles) (prepared as described in Preparative Example 57, Step D) (INO972), 1-[3-dimethylaminopropyl]-3-ethylcarbodiimide hydrochloride (0.524g, 2.73mmoles), 1-hydroxybenzotriazole
- 15 (0.3693g, 2.73mmoles) and 4-methylmorpholine (0.2765g, 0.3005mL, 2.73mmoles) were dissolved in anhydrous DMF (3mL) and the mixture was stirred under argon at 25°C for 122h. The mixture was evaporated to dryness and chromatographed on silica gel using 2-3%(10% conc. ammonium hydroxide in methanol)-
- 20 dichloromethane as the eluant to give the title compound (0.3127g, 30%): CIMS: m/z 492.4 (MH⁺); δ_H (CDCl₃) 1.47 (18H, s, CH₃), 7.01 (1H, s, Im-H₂), 7.05 (1H, s, Im-H₄) and 7.63ppm (1H, s, Im-H₅); δ_C (CDCl₃) CH₃: 28.2, 28.2, 28.2, 28.4, 28.4, 28.4; CH₂: 19.1, 25.9, 26.2, 31.9, 40.8/41.3, 41.7, 43.0, 44.0; CH: 46.0, ~52.1, 128.4,
- 25 137.2; C: ~80.4, 80.6, ~154.3, ~154.3 and ~169.8.

Step B

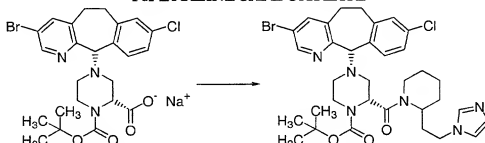
2(R)-[[2-[2-(1H-IMIDAZOL-1-YL)ETHYL]-1-PIPERIDINYL]CARBONYL]PIPERAZINE



- 5 The title compound from Step A above was deprotected as described in Preparative Example 57, Step D and chromatographed on silica gel to give the title compound.

EXAMPLE 138

- 10 1,1-DIMETHYLETHYL 4-(3-BROMO-8-CHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11(S)-YL)-2(R)-[[2-[2-(1H-IMIDAZOL-1-YL)ETHYL]-1-PIPERIDINYL]CARBONYL]-1-PIPERAZINECARBOXYLATE



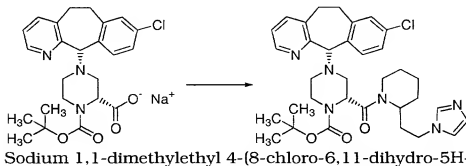
- 15 Sodium 1,1-dimethylethyl 4-(3-bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11(S)-yl)-2(R)-carboxy-1-piperazinecarboxylate (prepared as described in Preparative Example 6 (sodium salt)) (0.1g, 0.179mmoles), 2-[2-(1H-imidazol-1-yl)ethyl]piperidine (prepared as described in Preparative Example 57, Step D) (0.0417g, 0.233mmoles), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.0446g, 0.233mmoles), 1-hydroxybenzotriazole (0.0314g, 0.233mmoles) and 4-methylmorpholine (0.0512mL, 0.466mmoles) were dissolved in anhydrous DMF (4mL) and the mixture was stirred under argon at 25°C for 42h. The solution was evaporated to dryness and the residue was taken up in dichloromethane and washed with 1N NaOH, dried (MgSO₄), filtered and evaporated to dryness. The residue was chromatographed on silica gel using 2.5%-4.5%-7.5%
- 20
- 25

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(10% conc. NH_4OH in methanol)-dichloromethane as the eluant to give the title compound (0.0172g, 14%): HRFABMS: m/z 697.2285 (MH^+) (Calcd. m/z 697.2269); δ_{H} (CDCl_3) 1.38/1.41 (9H, s, CH_3), 4.31 (1H, s, H_{11}), 4.68 (1H, bs, H_2), 7.03-7.20 (5H, bm, Ar-H and Im-H₄ and Im-H₅), 7.57 (1H, s, Im-H₃), 7.83/8.19 (s, Ar-H) and 8.38ppm (1H, s, Ar-H₂); δ_{C} (CDCl_3) CH_3 : 28.4, 28.4, 28.4; CH_2 : 19.1, 24.8/24.9, 28.3, 30.3, 30.5, 31.4, 40.3, 42.9/43.2, 44.1/44.6, 45.6, 50.2/50.5; CH: 44.1/44.6, 52.4, 78.4, 119.2, 126.2, 127.9, 130.8/130.9, 132.6, 136.7, 141.6, 146.9/147.2; C: 80.4, 119.8/120.2, 134.4, 135.9, 137.0, 141.5, 155.0, 156.7/157.1, 170.3/170.9.

EXAMPLE 139

1,1-DIMETHYLETHYL 4-(8-CHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11(S)-YL)-2(R)-[[2-[2-(1H-IMIDAZOL-1-YL)ETHYL]-1-PIPERIDINYL]CARBONYL]-1-PIPERAZINECARBOXYLATE

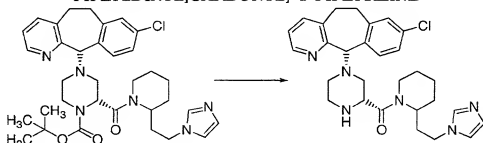


benzo[5,6]cyclohepta[1,2-b]pyridin-11(S)-yl)-2(R)-carboxy-1-piperazinecarboxylate (prepared as described in Preparative Example 6 (sodium salt)) (0.5239g, 1.09mmoles), 2-[2-(1H-imidazol-1-yl)ethyl]piperidine (prepared as described in Preparative Example 57, Step D) (0.2544g, 1.42mmoles), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.272g, 1.42mmoles), 1-hydroxybenzotriazole (0.1918g, 1.42mmoles) and 4-methylmorpholine (0.156mL, 1.42mmoles) were dissolved in anhydrous DMF (23.5mL) and the mixture was stirred under argon at 25°C for 286h. The solution was evaporated to dryness and the residue was taken up in dichloromethane and washed with 1N

NaOH, dried (MgSO₄), filtered and evaporated to dryness. The residue was chromatographed on silica gel using 2.5% (10% conc. NH₄OH in methanol)-dichloromethane as the eluant to give the title compound (0.2298g, 32%); HRFABMS: m/z 619.3169 (MH⁺) (Calcd. m/z 691.3163).

EXAMPLE 140

4-(8-CHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11(S)-YL)-2(R)-[[2-[2-(1H-IMIDAZOL-1-YL)ETHYL]-1-PIPERIDINYL]CARBONYL]-1-PIPERAZINE

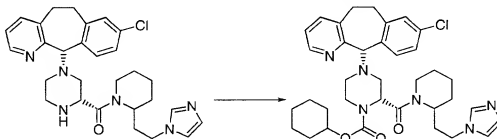


The title compound from Example 2 (0.225g, 0.363mmoles)

was dissolved in methanol (2mL). A 10% (v/v) solution of conc. H₂SO₄ in dioxane (v/v) (4.92mL) was added and the mixture was stirred at 25°C for 30h. The mixture was diluted with methanol (300mL) and then treated with BioRad AG1-X8 (OH⁻) resin until it was basic. The resin was filtered off and washed with methanol. The combined filtrates were evaporated to dryness and the residue was chromatographed on silica gel using 4% (10% conc. NH₄OH in methanol)-dichloromethane as the eluant to give the title compound (0.1692g, 90%); HRFABMS: m/z 519.2655 (MH⁺) (Calcd. m/z 519.26390), δ_H (CDCl₃) 4.43 (1H, s, H₁₁), 6.89, 6.93, 7.00, 7.10, 7.13, 7.19, 7.21, 7.43, 7.45, 7.50, 7.58, 8.03, 8.30 and 8.33ppm (8H, Ar-H and Im-H); δ_C (CDCl₃) CH₂: 19.0/19.1, 25.0/25.7/26.1, 28.3/29.0, 30.7/30.8, 30.9/31.0, 31.5/31.9, 40.0/40.7, 43.5, 44.1/44.2/44.4, 49.3, 51.5/52.3; CH: 45.7/46.1, 54.4/55.8, 79.5/79.7, 118.3/118.9, 123.1, 126.1/126.2, 129.1/129.5/129.7, 130.4/130.5, 132.7/132.8, 137.0/137.5, 138.9, 146.3; C: 134.0, 134.9, 135.5, 141.3, 157.1 and 169.8/170.5.

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EXAMPLE 141

CYCLOHEXYL 4-(8-CHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11(S)-YL)-2(R)-[[2-[2(R/S)-(1H-IMIDAZOL-1-YL)ETHYL-1-PIPERIDINYL]CARBOXYL]-1-PIPERAZINECARBOXYLATE



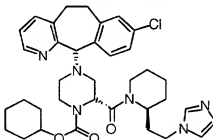
The title compound from Example 3 (0.165g, 0.318mmoles) and triethylamine (0.1329mL, 0.954mmoles) were dissolved in anhydrous dichloromethane (5mL). Cyclohexylchloroformate (0.0517g, 0.318mmoles) dissolved in anhydrous dichloromethane (3.18mL) was added and the mixture was stirred at 25°C for 18h. Additional cyclohexylchloroformate (0.0129g, 0.0795mmoles) was added and the stirring was continued for a total of 43h. Methanol (10mL) was added and the mixture was evaporated to dryness. The residue was chromatographed on silica gel using 2% (10% conc. NH₄OH in methanol)-dichloromethane as the eluant to give the title compound (0.153g, 75%): HRFABMS: m/z 645.3323 (MH⁺) (Calcd. MH⁺ for C₃₆H₄₆N₆O₃Cl: m/z 645.3320).

EXAMPLE 142

CYCLOHEXYL 4-(8-CHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11(S)-YL)-2(R)-[[2-[2(S)-(1H-IMIDAZOL-1-YL)ETHYL-1-PIPERIDINYL]CARBONYL]-1-

5

PIPERAZINECARBOXYLATE

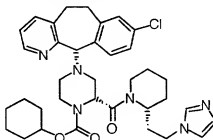


Isomer 1

and

10

(-)-CYCLOHEXYL 4-(8-CHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11(S)-YL)-2(R)-[[2-(R)-(1H-IMIDAZOL-1-YL)ETHYL-1-PIPERIDINYL]CARBONYL]-1-PIPERAZINECARBOXYLATE



Isomer 2

15

The diastereoisomeric mixture of compounds from Example 4 (0.154g) was separated using chiral HPLC on a Chiralpak AD[®] analytical column using hexane:iso- propanol:

diethylamine::85:15:0.2 as the eluant to give firstly isomer 1

20

(0.0376g): HRFABMS: m/z 645.3305 (MH⁺) (Calcd. MH⁺ for C₃₆H₄₅N₆O₃Cl: m/z 645.3320); δ_H (CDCl₃) 4.30 (1H, s, H₁₁), 6.69, 7.00, 7.08, 7.11, 7.16, 7.18, 7.42, 7.70, 8.32ppm (9H, s and m, Ar-H and Im-H); δ_C(CDCl₃) CH₂: 18.9, 23.6, 23.6, 24.8/25.1, 25.5, 28.0/28.2, 30.7/30.8, 30.9, 31.4, 31.8, 31.8, 42.7, 43.9/44.2, 50.9, 52.7; CH: 49.9/50.5, 52.3, 73.6, 79.3/79.9, 119.1/119.3, 123.3, 126.0, 128.7, 132.8, 137.1, 139.0/139.3, 146.3/146.9; C: 134.0, 135.1, 136.4, 141.8/142.0, 156.1, 157.0 and 170.1; [α]_D^{20°C} 0°

25

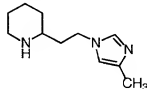
(c=6.89mg/2mL, MeOH) and then isomer 2 (0.0867g): HRFABMS:

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m/z 645.3305 (MH⁺) (Calcd. MH⁺ for C₃₆H₄₀N₆O₃Cl: m/z 645.3320);
 δ_H (CDCl₃) 4.34 (1H, s, H₁₁), 6.93, 6.99, 7.06, 7.12, 7.17, 7.21, 7.43,
 7.70 and 8.33ppm (9H, s and m, Ar-H and Im-H); δ_C (CDCl₃) CH₂:
 19.1, 23.5, 23.5, 24.7/24.8, 25.5, 28.9, 30.6/30.8, 31.5, 31.7, 31.7,
 36.7, 40.4, 42.8, 44.1, 50.5, 52.5; CH: 45.9, 52.3, 73.7, 79.2/79.4,
 119.4, 123.4, 126.0, 128.1, 130.7, 132.7, 137.1, 139.4,
 146.3/146.9; C: 134.1, 135.1, 136.6, 142.0, 156.1, 157.0 and
 170.2; $[\alpha]_D^{20^\circ C}$ -44.1° (c=10.05mg/2mL, MeOH). An overlap cut
 consisting of a mixture of isomer 1 and isomer 2 was also obtained
 (0.0196g).

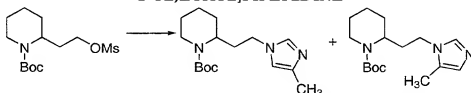
PREPARATIVE EXAMPLE 72

2(R/S)-[2-(1H-4-METHYLIMIDAZOL-1-YL)ETHYL]PIPERIDINE



15 Step A

1N-tert-BUTOXYCARBONYL-2(R/S)-[2-(1H-4/5-METHYLIMIDAZOL-1-YL)ETHYL]PIPERIDINE

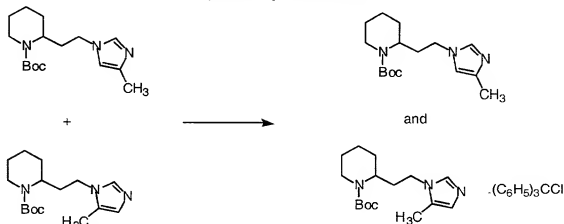


4-Methylimidazole (6.46g, 78.64mmoles) was dissolved
 in anhydrous DMF (300mL) and 95% sodium hydride (1.987g,
 86.5mmoles) was added in portions over 0.25h to the stirred
 solution at 25°C under argon. The mixture was stirred for 1.5h. A
 solution of 1-tert-butoxycarbonyl-2(R/S)-[2-
 methanesulfonyloxyethyl]piperidine (21.97g, 71.49mmoles)
 (prepared as described in Preparative Example 57, Step B) in
 anhydrous DMF (70mL) was added and the mixture was heated
 under reflux at 65°C for 2.25h. The mixture was evaporated to
 dryness and the residue was taken up in dichloromethane and
 washed with water, dried (MgSO₄), filtered and evaporated to

dryness. The product was chromatographed on silica gel using 1% (10% conc. NH_4OH in methanol)-dichloromethane to give a mixture of the title compounds (12.06g, 58%) (4-Me:5-Me::63:37): CIMS: m/z 294.25 (MH^+); 4-Me: δ_{H} (CDCl_3) 1.43 (9H, s, CH_3), 2.20 (3H, s, Im-4- CH_3), 6.63 (1H, s, Im- H_5) and 7.35ppm (1H, s, Im- H_2); δ_{C} (CDCl_3) CH_3 : 13.6, 28.4, 28.4, 28.4; CH_2 : 19.0, 25.4, 28.7, 31.6, 38.8, 44.1; CH: 48.0, 115.2, 136.1; C: 79.7, 138.3, 155.0 and 5-Me: δ_{H} (CDCl_3) 1.43 (9H, s, CH_3), 2.19 (3H, s, Im-5-Me), 6.75 (1H, s, Im- H_4) and 7.41ppm (1H, s, Im- H_2); δ_{C} (CDCl_3) CH_3 : 9.2, 28.4, 28.4, 28.4; CH_2 : 19.0, 25.4, 28.7, 31.4, 38.8, 42.0; CH: 48.0, 126.9, 136.5; C: 79.7, 138.3, 155.0.

Step B

1N-tert-BUTOXYCARBONYL-2(R/S)-[2-(1H-4-METHYLIMIDAZOL-1-YL)ETHYL]PIPERIDINE



The mixture of compounds from Step A above (1.77g) was dissolved in anhydrous CH_2Cl_2 (18.6mL) at 0°C under argon. Trityl chloride (1.2445g, 2 equivalents per equivalent of the 5-methyl isomer) was added and the mixture was stirred at 0°C for 2h. The reaction mixture was introduced directly onto a silica gel column and the column was eluted with 50% ethyl acetate in acetone to give the pure 4-methyl isomer (0.6267g, 56%): 4-Me: δ_{H} (CDCl_3) 1.44 (9H, s, CH_3), 2.20 (3H, s, Im-4- CH_3), 6.64 (1H, s, Im- H_5) and 7.36ppm (1H, s, Im- H_2); δ_{C} (CDCl_3) CH_3 : 13.7, 28.5, 28.5, 28.5; CH_2 : 19.1,

- 180 -
25.5, 28.9, 31.7, 39.0, 44.2; CH: 48.1, 115.1, 136.2; C: 79.8, 138.4, 155.1.

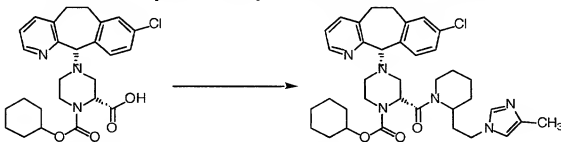
Step C

5 2(R/S)-[2-(1H-4-METHYLIMIDAZOL-1-YL)ETHYL]PIPERIDINE

The pure 4-methyl isomer (0.7518g, 2.56mmoles) was deprotected as described in Preparative Example 57, Step D, to give after purification, the title compound (0.4366g, 88%): FABMS: m/z 194.2 (MH⁺); δ_H (CDCl₃) 1.76 (2H, m, CH₂), 2.19 (3H, s, Im-4-CH₃), 3.94 (2H, m, CH₂-Im), 6.60 (1H, s, Im-H₃) and 7.33ppm (1H, s, Im-H₂); δ_C(CDCl₃) CH₃: 13.7; CH₂: 24.5, 26.6, 32.9, 38.4, 43.6, 46.8; CH: 53.9, 115.2, 136.2; C: 138.4.

EXAMPLE 143

15 CYCLOHEXYL 4-(8-CHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11(S)-YL)-2(R)-[[2-[2(R/S)-(4-METHYL-1H-IMIDAZOL-1-YL)ETHYL]-1-PIPERIDINYL]CARBONYL]-1-PIPERAZINECARBOXYLATE



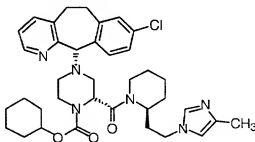
20 Cyclohexyl 4-(8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11(S)-yl)-2(R)-carboxy-1-piperazinecarboxylate (0.275g, 0.568mmoles) (prepared as described in Preparative Example 32), 2-[2(R/S)-(4-methyl-1H-imidazol-1-yl)ethyl]piperidine (0.1428g, 0.7386mmoles) (prepared as described in Preparative Example 2, Step C), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.1416g, 0.7386mmoles), 1-hydroxybenzotriazole (0.0998g, 0.7386mmoles) and 4-methylmorpholine (0.0812mL, 0.7386mmoles) were dissolved in anhydrous DMF (12.2mL) and the mixture was stirred at 25°C for 212h under argon. The solution was evaporated to dryness and

30

taken up in dichloromethane and washed with 1N NaOH. The aqueous layer was extracted 3X with dichloromethane (200mL) and the combined organic layers were dried (MgSO₄), filtered and evaporated. The product was chromatographed on silica gel using 2% (10% conc. NH₄OH in methanol)-dichloromethane as the eluant to give the title compound (0.149g, 40%): FABMS: m/z 659.62 (MH⁺).

EXAMPLE 144

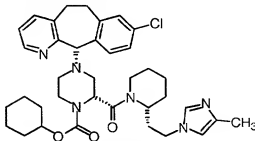
(-)-CYCLOHEXYL 4-(8-CHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11(S)-YL)-2(R)-[[2-[2(S)-(4-METHYL-1H-IMIDAZOL-1-YL)ETHYL]-1-PIPERIDINYL]CARBONYL]-1-PIPERAZINECARBOXYLATE



Isomer 1

and

(-)-CYCLOHEXYL 4-(8-CHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11(S)-YL)-2(R)-[[2-[2(R)-(4-METHYL-1H-IMIDAZOL-1-YL)ETHYL]-1-PIPERIDINYL]CARBONYL]-1-PIPERAZINECARBOXYLATE



Isomer 2

The diastereoisomeric mixture of compounds from Example 6 (0.145g) was separated using chiral HPLC on a Chiralpak AD[®] analytical column using hexane:*iso*-propanol: diethylamine::70:30:0.2 as the eluant to give firstly isomer 1

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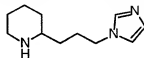
(0.0475g); FABMS: m/z 659.4 (MH⁺); δ_H (CDCl₃) 1.66 (2H, m, CH₂), 2.23 (3H, s, Im-4-CH₃), 3.71 (2H, m, CH₂-Im), 4.32 (1H, s, H₁₁), 6.58, 6.72, 6.75, 7.10, 7.14, 7.20, 7.41, 7.60 and 8.34ppm (9H, s and m, Ar-H and Im-H); δ_C (CDCl₃) CH₃: 13.4/13.7; CH₂: 18.9, 23.5, 23.5, 24.2/25.1, 25.5, 28.1, 30.7, 30.8, 31.4, 31.8, 31.8, 36.7, 42.4/42.6, 43.8/44.1, 50.5/50.8, 52.8; CH: 49.8, 52.3, 73.6, 79.3/80.0, 115.5/115.8, 123.3, 126.0, 130.6/130.8, 132.8, 136.0, 139.2/139.3, 146.3; C: 134.0, 135.0/135.1, 136.2/136.5, 137.8, 141.8/142.0, 156.1, 157.0, 170.1; [α]_D^{20°C} -4.3° (c=8.07mg/2mL,

10 MeOH), and then isomer 2 (0.852g): HRFABMS: m/z 659.3492 (MH⁺) (Calcd. MH⁺ for C₃₇H₄₅N₆O₃Cl: m/z 659.3476); δ_H (CDCl₃) 1.64 (2H, m, CH₂), 2.22 (3H, s, Im-4-CH₃), 3.72 (2H, m, CH₂-Im), 4.35 (1H, s, H₁₁), 6.61, 6.67, 7.12, 7.17, 7.22, 7.43, 7.57 and 8.35ppm (9H, s and m, Ar-H and Im-H); δ_C (CDCl₃) CH₃: 13.3/13.5; CH₂: 19.1, 23.5, 23.5, 24.7, 25.5, 28.7/28.9, 30.6, 30.8, 31.5, 31.7, 31.7, 40.3, 42.1/42.8, 44.1/44.2, 50.5/50.7, 52.6/52.7; CH: 46.0/46.2, 52.5, 73.7, 79.3/79.4, 115.6/115.8, 123.4, 126.0, 130.7, 132.7, 136.0/136.2, 139.4, 146.3; C: 134.1, 135.1, 136.2/136.6, 137.2, 142.0, 156.1, 157.1, 170.3; [α]_D^{20°C} -44.7° (c=9.0mg/2mL, MeOH).

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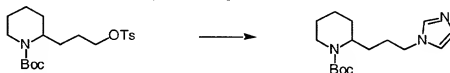
PREPARATIVE EXAMPLE 73

2(R/S)-[3-(1H-IMIDAZOL-1-YL)PROPYL]PIPERIDINE



Step A

25 1N-tert-BUTOXYCARBONYL-2(R/S)-[3-(1H-IMIDAZOL-1-YL)PROPYL]PIPERIDINE



The title compound from Preparative Example 58, Step C, (1.29g, 4.3mmoles) was dissolved in anhydrous DMF (15mL).

30 Sodium imidazole (0.3215g, 4.7mmoles) was added and the mixture

was stirred at 25°C under argon for 3h. The solution was evaporated to dryness and the residue was chromatographed on silica gel using 2% (10% conc. NH_4OH in methanol)-dichloromethane as the eluant to give the title compound (0.6813g, 72%): CIMS: m/z 294.25 (MH^+); δ_{H} (CDCl_3) 1.43 (9H, s, CH_3), 3.97 (2H, m, $\text{CH}_2\text{-Im}$), 6.90 (1H, s, Im- H_9), 7.04 (1H, s, Im- H_7) and 7.45ppm (1H, s, Im- H_2); δ_{C} (CDCl_3) CH_2 : 28.4, 28.4, 28.4; CH_2 : 18.9, 25.4, 26.3, 27.7, 28.6, 38.8, 46.5; CH: ~49.0, 118.6, 129.4, 137.1; C: 79.3, 155.0.

Step B

2(R/S)-[3-(1H-IMIDAZOL-1-YL)PROPYL]PIPERIDINE



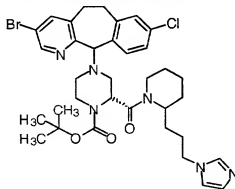
The title compound from Step A above (0.6075g, 2.1mmoles)

was deprotected as described in Preparative Example 57, Step D, and chromatographed on silica gel using 10% (10% conc. NH_4OH in methanol)-dichloromethane as the eluant to give the title compound (0.3805g, 95%): CIMS: m/z 194.20 (MH^+); δ_{H} (CDCl_3) 3.89 (2H, m, $\text{CH}_2\text{-Im}$), 6.84 (1H, s, Im- H_9), 6.99 (1H, s, Im- H_7) and 7.41ppm (1H, s, Im- H_2); δ_{C} (CDCl_3) CH_2 : 24.9, 26.7, 27.2, 33.1, 34.4, 47.2, 47.2; CH: 56.4, 118.8, 129.6, 137.1.

EXAMPLE 145

1,1-DIMETHYLETHYL 4-(3-BROMO-8-CHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YL)-2(R)-[[2-[3-(1H-IMIDAZOL-1-YL)PROPYL]-1-PIPERIDINYL]CARBONYL]-1-

PIPERAZINECARBOXYLATE



Isomers 1, 2, 3 and 4.

1,1-dimethylethyl 4-(3-bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-2(R)-carboxy-1-

piperazinecarboxylate (0.7225g, 1.3mmoles) (prepared as described in Preparative Example 6), the title compound from Preparative Example 8, Step B (0.3382g, 1.7mmoles), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.3354g, 1.7mmoles), 1-hydroxybenzotriazole (0.2364g, 1.7mmoles) and 4-

methylmorpholine (0.192mL, 1.7mmoles) were dissolved in anhydrous DMF (3mL) and the mixture was stirred under argon at 25°C for 319h. The solution was evaporated to dryness and the residue was taken up in dichloromethane and washed with saturated aqueous sodium bicarbonate, water, dried (MgSO₄),

filtered and evaporated to dryness. The residue was chromatographed on silica gel using 3% (10% conc. NH₄OH in methanol)-dichloromethane as the eluant to give the partially purified title compounds. The appropriate fractions were

rechromatographed using 1.5% (10% conc. NH₄OH-methanol)-dichloromethane as the eluant to give title compound as a mixture of 4 diastereoisomers (0.3718g, 39%): FABMS: m/z 711.4 (MH⁺); δ_H (CDCl₃) 1.39 (9H, s, CH₃), 6.91, 7.08, 7.13, 7.17, 7.56, 7.67 (Ar-H), 6.97 (1H, s, Im-H₉), 7.04 (1H, s, Im-H₉), 7.58 (1H, s, Im-H₂) and

8.38ppm (1H, m, Ar-H₂); δ_c (CDCl₃) CH₃: 28.3/28.4, 28.3/28.4, 28.3/28.4; CH₂: 18.9, 24.9/25.0/25.5, 26.8, 30.2, 30.5, 36.2, 40.1, 42.7/43.0, 46.5/46.7, 50.1/50.3/50.7, 52.7/52.9; CH: 46.9, 51.6/52.0, 78.5, 119.0, 126.2/126.3, 128.6, 130.8/130.9, 132.6, 137.0, 141.5, 146.9/147.2; C: 80.2, ~120.1, 134.3, 134.9, 137.6, 140.8, ~155.1/156.1, ~156.8, ~170.3.

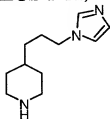
A portion of the diastereomeric mixture (0.28g) was subjected to chiral HPLC on a Chiralpak[®] AD column using hexane:iso-propanol: diethylamine::85:15:0.2 as the eluant to give only a partial separation. Isomer 1 (0.0604g) was obtained pure while isomers 3 and 4 (0.0376g) were obtained as a 97% pure mixture. The remaining overlap cuts could not be separated.

Isomer 1: HRFABMS: m/z 711.2429 (MH⁺) (Calcd. MH⁺ for C₃₈H₄₅N₆O₃BrCl: m/z 711.2425); δ_H (CDCl₃) 1.41 (9H, s, CH₃), 4.29 (1H, s, H₁₁), 6.92, 7.14, 7.18, 7.20 (Ar-H), 6.98 (1H, s, Im-H₃), 7.08 (1H, s, Im-H₄), 7.58 (1H, s, Im-H₂), 7.63 (1H, s, Ar-H₄) and 8.38ppm (1H, s, Ar-H₂); δ_c (CDCl₃) CH₃: 28.3, 28.3, 28.3; CH₂: 18.9, 24.7, 25.4, 26.7, 28.8, 30.3, 30.5, 40.2, 43.1, 46.6, 50.6/50.7, 52.6; CH: 46.9/47.1, 52.1, 78.5/78.6, 119.1, 126.2, 128.3, 130.9, 132.6, 136.9, 141.5, 146.9/147.2; C: 79.7/80.2, 120.2, 133.6, 134.2, 136.9, 136.9, 155.1, 156.7, 170.2; $[\alpha]_D^{20} -22.2^\circ$ (c=6.74mg/2mL, MeOH).

Isomers 3 and 4: FABMS: m/z 711.3 (MH⁺); δ_H (CDCl₃) 1.39, 1.42 (9H, s, CH₃), 4.27, 4.29 (1H, s, H₁₁), 6.85, 6.91, 7.05, 7.12-7.18, 7.43 (Ar-H), 6.98 (1H, s, Im-H₃), 7.08 (1H, s, Im-H₄), 7.56 (1H, s, Im-H₂), 7.60, 7.71 (1H, s, Ar-H₄) and 8.38ppm (1H, s, Ar-H₂); δ_c (CDCl₃) CH₃: 28.3/28.4, 28.3/28.4, 28.3/28.4; CH₂: 18.8, 25.2, 25.3, 26.8, 28.6, 30.2, 30.4/30.5, 36.4, 42.8, 46.6, 50.5, 52.7/53.3; CH: 46.9/47.2, 51.6/52.2, 78.5/78.6, 119.2, 126.2, 128.6, 130.7/130.8, 132.6, 137.0, 141.5, 146.9; C: 80.1, 80.1, 120.0, 134.4, 134.8, 137.5/137.6, 141.0, 156.1, 156.6, 156.6, 170.0/170.2, 170.0/170.2.

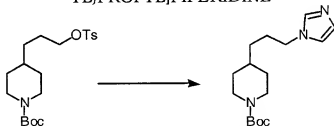
PREPARATIVE EXAMPLE 74

4-[3-(1H-IMIDAZOL-1-YL)PROPYL]PIPERIDINE



Step A

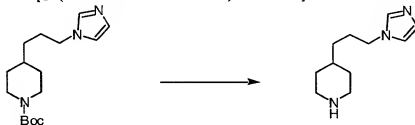
5 1N-tert-BUTOXYCARBONYL-4-[3-(1H-IMIDAZOL-1-YL)PROPYL]PIPERIDINE



The title compound from Preparative Example 59, Step C (1.39g, 3.5mmoles) was dissolved in anhydrous DMF (10mL) and sodium imidazole (0.3464g, 3.85mmoles) was added and the mixture was stirred at 25°C for 3h under argon. The solution was evaporated to dryness and the residue was chromatographed on silica gel using 2% (10% conc. NH_4OH in methanol)-dichloromethane as the eluant to give the title compound (0.7637g, 74%): FABMS: m/z 294.20 (MH^+); δ_{H} (CDCl_3) 1.39 (9H, s, CH_3), 3.88 (2H, m, $\text{CH}_2\text{-Im}$), 6.85 (1H, s, Im-H_5), 7.00 (1H, s, Im-H_4) and 7.40ppm (1H, s, Im-H_2); δ_{C} (CDCl_3) CH_3 : 28.5, 28.5, 28.5; CH_2 : 28.3, 32.0, 33.3, 33.3, 44.0, 44.0, 47.2, 118.7, 129.5, 137.1; CH: 35.7; C: 79.3, 154.8.

Step B

4-[3-(1H-IMIDAZOL-1-YL)PROPYL]PIPERIDINE

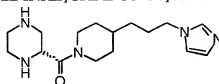


The title compound from Preparative Example 4, Step A above was deprotected as described in Preparative Example 57, Step D, to

give after chromatography on silica gel using 20% (10% conc. NH_4OH in methanol)-dichloromethane as the eluant, the title compound (0.4346g, 95%): CIMS: m/z 194.20 (MH^+); δ_{H} (CDCl_3) 3.89 (2H, m, $\text{CH}_2\text{-Im}$), 6.88 (1H, s, Im-H_9), 7.02 (1H, s, Im-H_4) and 7.42ppm (1H, s, Im-H_5); δ_{C} (CDCl_3) CH_2 : 28.3, 33.5, 33.5, 34.1, 46.7, 46.7, 47.4; CH: 36.0, 118.8, 129.6, 137.2.

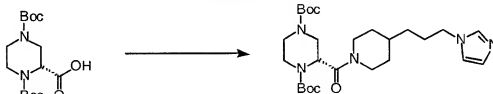
PREPARATIVE EXAMPLE 75

2(R)-[[4-[3-(1H-IMIDAZOL-1-YL)PROPYL]-1-PIPERIDINAL]CARBONYL]PIPERAZINE



Step A

1,4-BIS-1,1-DIMETHYLETHYL 2(R)-[[4-[3-(1H-IMIDAZOL-1-YL)PROPYL]-1-PIPERIDINYL]CARBONYL]PIPERAZINE-1,4-BIS-CARBOXYLATE



1,4-Di-N-tert-butoxycarbonylpiperazine-2(R)-carboxylate

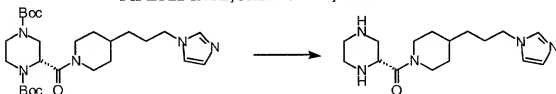
(0.521g, 1.6mmoles) (prepared as described in Preparative Example 2), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.393g, 2.1mmoles), 1-hydroxybenzotriazole (0.0277g, 2.1mmoles) and 4-methylmorpholine (0.225mL, 2.1mmoles) were dissolved in anhydrous DMF (3mL) and the mixture was stirred under argon at 25°C for 150h. The solution was evaporated to dryness and the residue was taken up in dichloromethane and washed with saturated aqueous sodium bicarbonate, water, dried (MgSO_4), filtered and evaporated to dryness. The residue was chromatographed on silica gel using 3% (10% conc. NH_4OH in methanol)-dichloromethane as the eluant to give the title compound (0.693g, 87%): CIMS: m/z 506.35 (MH^+); δ_{H} (CDCl_3) 1.42 (18H, s, CH_3), 3.91 (2H, m, $\text{CH}_2\text{-Im}$), 6.88 (1H, s, Im-H_9), 7.03 (1H, s, Im-H_4)

and 7.43ppm (1H, s, Im-H₂); δ_c(CDCl₃) CH₃: 28.4, 28.4, 28.4, 28.4, 28.4, 28.4; CH₂: 28.4, 31.8, 33.1, 33.1, 41.2/41.6, 43.8, 43.8, 45.6, 47.1, ~51.0; CH: 35.8, 52.9, 118.7, 129.6, 137.1; C: 80.1, 80.4, 168.1, 168.1 168.1.

5

Step B

2(R)-[[4-[3-(1H-IMIDAZOL-1-YL)PROPYL]-1-PIPERIDINYL]CARBONYL]PIPERAZINE



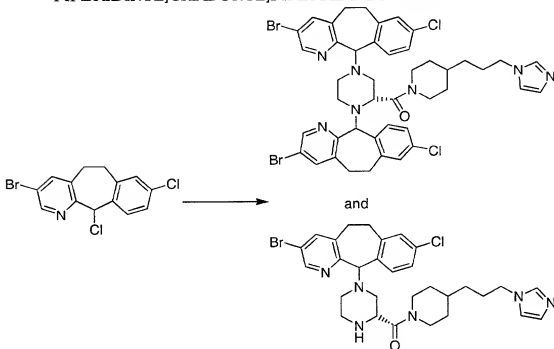
10 The title compound from Preparative Example 5, Step A above (0.6344g, 1.26mmoles) was deprotected as described in Preparative Example 57, Step D, and the product was chromatographed on silica gel using 10% (10% conc. NH₄OH in methanol)-dichloromethane as the eluant to give the title compound (0.3076g, 80%): CIMS: m/z 306.30 (MH⁺); δ_H (CDCl₃) 3.87 (2H, m, CH₂-Im), 6.82 (1H, s, Im-H₂), 6.99 (1H, s, Im-H₄) and 7.38ppm (1H, s, Im-H₂); δ_c(CDCl₃) CH₂: 28.1, 31.7, 32.6/32.9, 33.0/33.1, 42.0/42.2, 45.2/45.5, 46.9/47.0, 46.9/47.0, 46.9; CH: 35.7/35.8, 55.6, 118.7, 129.4, 137.0; C: 169.7.

20

EXAMPLE 146

4-(3-BROMO-8-CHLORO-6,11-DIHYDRO-5H-
BENZO[5,6]CYCLOHEPTA[1,2-

b)PYRIDIN-11-YL)-2(R)-[[4-[3-(1H-IMIDAZOL-1-YL)PROPYL]-1-
PIPERIDINYL]CARBONYL]PIPERAZINECARBOXYLATE



3-Bromo-8,11-dichloro-6,11-dihydro[5,6]cyclohepta[1,2-

b)pyridine (0.2043g, 0.596mmoles) (prepared as described in
Preparative Example 40 (U.S. 5,719,148)), the titled compound from

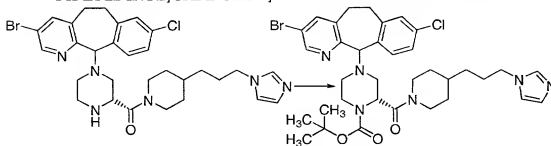
- 10 Preparative Example 5, Step B (0.2729g, 0.894mmoles) and
triethylamine (0.249mL, 1.79mmoles) were dissolved in anhydrous
THF (8mL) and anhydrous dichloromethane (20mL) and the mixture
was stirred at 25°C for 72h under argon. The solution was
evaporated to dryness and the residue was chromatographed on
15 silica gel using 3% then 5% and the 10% (10% conc. NH₄OH in
methanol)-dichloromethane as the eluant to give first the dimer (Sch
377314) (0.0681g, 12%); SIMS: m/z 916.2 (MH⁺); δ_H (CDCl₃) 3.99
(4H, m, CH₂-Im), 6.95, 7.08, 7.10, 7.12, 7.26, 7.54, 7.69, 8.28, 8.31
and 8.34ppm (13H, s and m, Ar-H and Im-H); δ_C (CDCl₃) CH₂:
20 28.3/28.5, 30.3/30.4, 30.5, 31.3/31.5, 33.1, 33.1, 41.0/41.1,
41.0/41.1, 45.0, 47.5, 51.2/51.3/52.0, 53.9/54.1/54.2; CH: 35.7,
78.8/79.0, 119.7/119.9, 125.9/126.0/126.2, 128.6/128.7, 130.7,
133.8/134.1, 136.9/137.6, 141.5, 146.7/146.9; C: 119.0, 130.0,

- 190 -

132.5/133.2, 134.6, 141.1/141.3, 156.2, 156.8, 170.0 and the then monomer (Sch 377318) (0.2291g, 63%): CIMS: m/z 611.20 (MH^+); δ_H ($CDCl_3$) 3.93 (2H, m, CH_2 -Im), 6.90, 6.92, 7.07, 7.12, 7.14, 7.47, 7.49, 7.57, 7.59, 8.33, 8.35 and 8.38ppm (8H, s and m, Ar-H and Im-H); δ_C ($CDCl_3$) CH_2 : 28.3, 30.6, 30.6, 31.6/31.7/31.9, 33.1/33.3, 33.1/33.3, 41.6/42.2, 44.4/44.9, 44.4/44.9, 45.3/45.7, 47.2, 52.2/52.7, 55.0; CH: 35.6, 55.4, 78.8, 118.8, 126.2/126.3, 129.6, 130.3/130.6, 133.0/133.2, 137.1, 141.3, 146.9/147.1; C: 120.1, 134.1, 135.0, 137.2, 141.1, 154.4/155.9, 169.0/170.0.

EXAMPLE 147

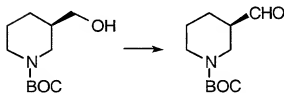
1,1-DIMETHYLETHYL 4-(3-BROMO-8-CHLORO-6,11-DIHYDRO-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDIN-11-YL)-2(R)-[4-[3-(1H-IMIDAZOL-1-YL)PROPYL]-1-PIPERIDINYL]CARBONYLPIPERAZINECARBOXYLATE



The title compound from Example 9 (0.1768g, 0.29mmoles) was reacted with di-tert-butylidicarbonate (0.0694g, 0.319mmoles) and sodium hydroxide (0.0116g, 0.29mmoles) in THF-water (1:1) (5mL) and purified as described in Preparative Example 57, to give the title compound (0.1294g, 63%): FABMS: m/z 711.1 (MH^+); δ_H ($CDCl_3$) 1.38/1.40 (9H, s, CH_3), 3.98 (2H, m, CH_2 -Im), 6.93, 7.03, 7.09, 7.18, 7.54, 7.58, 7.63, 8.32 and 8.38ppm (8H, s and m, Ar-H and Im-H); δ_C ($CDCl_3$) CH_3 : 28.4, 28.4, 28.4; CH_2 : 28.3, 30.2, 30.7, 31.3/31.8, 33.2, 33.2, 42.2/42.6, 44.4/45.4, 44.6, 44.6, 47.4, ~50.4, ~50.9; CH: 35.8, 78.6/78.8, 118.9, 126.3, 130.2, 130.8, 132.7, 137.0, 140.7/141.5, 147.2; C: 80.0, 119.9, 133.4, 134.0, 137.5, 141.4, 156.2, 156.2, 168.8.

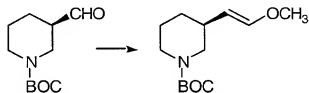
- 191 -
PREPARATIVE EXAMPLE 71A

Step A



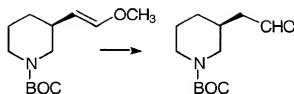
- To the title compound from Preparative Example 8, Step B
- 5 (1.63g, 7.57 mmol) in DMSO (5.0 mL) was added $i\text{Pr}_2\text{NEt}$ (6.59 mL, 5.0 eq.) followed by $\text{pyr} \cdot \text{SO}_3$ (7.23g, 3.0 eq.) in DMSO (10 mL). The resulting solution was stirred 1 hour, diluted with EtOAc and washed with 1N HCl, H_2O , and sat. NaHCO_3 . The organics were dried over Na_2SO_4 , filtered, and concentrated under reduced
- 10 pressure. The residue was used without purification (1.26g, 76% yield): LCMS: $\text{MH}^+ = 214$.

Step B



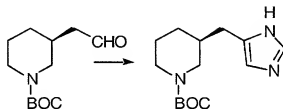
- 15 NaHMDS (14.7 mL, 1M in THF, 1.5 eq.) was added to a solution of $\text{CH}_3\text{OCH}_2\text{P}^+\text{Ph}_3\text{Cl}^-$ (5.06g, 1.5 eq.) in THF (25 mL) at 0°C . The resulting solution was stirred 15 minutes before adding *via* *canulae* to a solution of the title compound from Preparative Example 71A, Step A (2.1g, 9.80 mmol) in THF (25 mL) at -78°C .
- 20 The reaction mixture was stirred 1 hour at -78°C , warmed to 0°C and stirred 1 hour. The resulting solution was diluted with Et_2O , washed with H_2O , and dried over Na_2SO_4 . The organics were dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by flash chromatography using a 65 : 35 hexanes EtOAc
- 25 solution as eluent (1.51g, 64% yield).

Step C



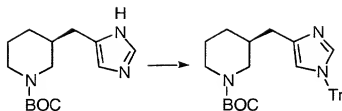
- The title compound from Preparative Example 71A, Step B (0.70g, 2.90 mmol) was stirred in 40% HCl (6.6 mL) at room temperature overnight at which time additional 40% HCl (3.0 mL) was added and the reaction mixture stirred an additional 4 hours. The resulting solution was neutralized with Na_2CO_3 (aq.) and extracted with Et_2O . The combined organics were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography using a 65 : 35 hexanes : EtOAc solution as eluent (0.30g, 46% yield + SM): LCMS: $\text{MH}^+=228$.

Step D



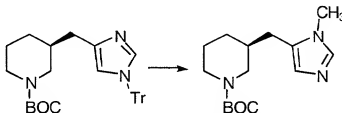
- The title compound from Preparative Example 71A, Step C (0.90g, 1.02 eq.) was stirred with TosMIC (0.77g, 3.88 mmol) and NaCN (0.0194g, 0.1eq.) in EtOH (7.0 mL) for 30 minutes. The reaction mixture was transferred to a sealed tube, diluted with 7M NH_3 in MeOH (13.0 mL) and heated to 90 °C for 22 hours. The resulting solution was cooled, concentrated under reduced pressure, diluted with 1N NaOH and extracted with CH_2Cl_2 . The combined organics were dried over Na_2SO_4 , filtered, and concentrated. The crude product was purified by flash chromatography using a 5% (10% NH_4OH in MeOH) solution in CH_2Cl_2 as eluent (0.53g, 51% yield): LCMS: $\text{MH}^+=266$.

Step E



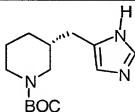
- The title compound from Preparative Example 71A, Step D (0.34g, 1.28 mmol) in CH_2Cl_2 was treated with TrCl (0.38g, 1.05 eq.) and TEA (0.27 mL, 1.5 eq.). The resulting solution was stirred 2 hours at room temperature, diluted with saturated NaHCO_3 , and extracted with CH_2Cl_2 . The combined organics were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography using a 3% (10% NH_4OH in MeOH) solution in CH_2Cl_2 as eluent (0.43g, 66%): LCMS: $\text{MH}^+=508$.

Step F



- The title compound from Preparative Example 71A, Step E (0.43g, 0.846mmol) in Et_2O was treated with MeI (0.79 mL, 15 eq.) and stirred overnight and filtered. The resulting solid washed with Et_2O , dissolved in MeOH and heated at reflux overnight. The reaction mixture was concentrated in *vacuo* and purified by flash chromatography using a 5% (10% NH_4OH in MeOH) solution in CH_2Cl_2 as eluent (0.14g, 79% yield): LCMS: $\text{MH}^+=280$.

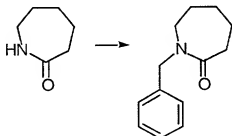
PREPARATIVE EXAMPLE 72A



By essentially the same procedure set forth in Preparative Example 71A, the title compound was prepared.

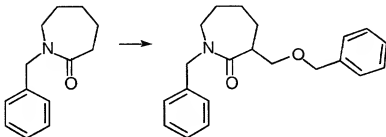
PREPARATIVE EXAMPLE 73A

5 Step A



- A solution of ϵ -caprolactam (6.86 g, 60 mmol, 1.0 eq.) in anhydrous THF (50 mL) was added dropwise over a period of 50 minutes to a stirred suspension of sodium hydride (1.59 g, 1.05 eq.) in anhydrous THF (20 mL) at 0 °C under a nitrogen atmosphere. The snow-white mixture was stirred at room temperature for 2h, whereupon a solution of benzyl bromide (7.65 mL, 1.05 eq.) in anhydrous THF (20 mL) was added dropwise over a period of 30 minutes. The mixture was stirred at room temperature for 2h and
- 10 filtered through CELITE 521 to remove sodium bromide. The volatiles were evaporated under house vacuum at 30 °C to give the title compound as a dark-yellow oil which was used without further purification (10.60 g, 87% yield). FABMS: MH⁺=204.

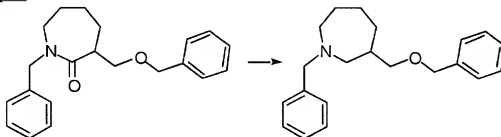
20 Step B



- A 2.45 M solution of *n*-butyllithium in hexanes (18.1 mL, 44.3 mmol, 1.44 eq.) was added dropwise over a period of 30 minutes to a stirred solution of diisopropylamine (5.2 mL, 36.9 mmol, 1.2 eq.) in anhydrous THF (100 mL) at 0 °C under a nitrogen atmosphere.
- 25

The yellow solution was stirred at 0 °C for another 30 minutes and was then cooled to -78 °C. A solution of the title compound from Preparative Example 73A, Step A (6.25 g, 1.0eq.) in anhydrous THF (50 mL) was subsequently added dropwise over a period of 25 minutes and the solution was stirred at -78 °C for another 3h. Neat benzyl chloromethyl ether (7.0 mL, 1.3 eq.) was added dropwise over a period of 10 minutes. The dirty-brown solution was slowly (3h) warmed to room temperature and stirred for another 12h. The volatiles were removed under house vacuum at 30 °C. The residual deep-yellow oil was partitioned between distilled water (100 mL) and diethyl ether (100 mL). The layers were separated and the aqueous phase was extracted with diethyl ether (5 x 50 mL). The organic layer of earlier and the ethereal extracts were combined and washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated under house vacuum at 30 °C. The oily residue was flash-chromatographed (hexanes:acetone = 8:2 v/v) over silica gel to give the title compound as a lime-green oil (6.77g, 68% yield). [M+H]⁺: 324; HRMS (FAB+): Calculated for C₂₁H₂₆NO₂ ([M + H]⁺): 324.1961; Observed: 324.1964.

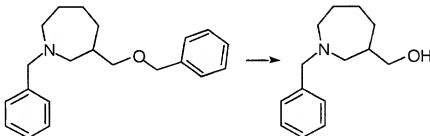
Step C



A 1 M solution of lithium aluminum hydride in diethyl ether (23 mL, 1.1 eq.) was added dropwise over a period of 25 minutes to a stirred solution of the title compound from Preparative Example 73A, Step B (6.77 g, 20.9 mmol) in anhydrous THF (100 mL) at -20 °C under a nitrogen atmosphere. The yellow solution was slowly (3h) warmed to room temperature and stirred for another 12h. The solution was cooled to 0 °C and carefully treated with a saturated,

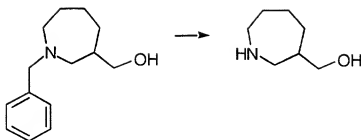
aqueous Na_2SO_4 solution (10 mL) to give a snow-white slurry. The mixture was filtered and the precipitate was carefully washed with diethyl ether (3 x 50 mL) and absolute alcohol (3 x 50 mL). The filtrate was concentrated under house vacuum at 30 °C, redissolved in acetone (100 mL) and dried over Na_2SO_4 , filtered, and again concentrated under house vacuum at 30 °C. The oily residue was flash-chromatographed (hexanes:acetone = 9:1 v/v) over silica gel to give the title compound as a lime-green oil (5.08 g, 78% yield): $[\text{M} + \text{H}]^+$: 310; HRMS (FAB+): Calculated for $\text{C}_{21}\text{H}_{28}\text{NO}$ ($[\text{M} + \text{H}]^+$): 310.2173; Observed: 310.2171.

Step D



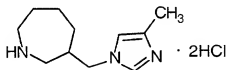
A mixture of the title compound from Preparative Example 73A, Step C (5.08 g, 16.4 mmol) 20 wt. % $\text{Pd}(\text{OH})_2$ ("Pearlman's catalyst," 2.54 g, 50 wt. % reagent), and absolute alcohol (100 mL) was hydrogenated at 4.5 atmosphere pressure and room temperature for 8h. The mixture was filtered through CELITE 521 and the filtrate was concentrated under house vacuum at 30 °C. The residual oil was flash-chromatographed (CH_2Cl_2 :10% NH_4OH -MeOH=9:1 v/v) over silica gel to give the title compound as a yellow oil (2.86 g, 79% yield): $[\text{M} + \text{H}]^+$: 220; HRMS (FAB+): Calculated for $\text{C}_{14}\text{H}_{22}\text{NO}$ ($[\text{M} + \text{H}]^+$): 220.1698; Observed: 220.1701.

Step E



- Potassium metal (2.60 g, 5.0 eq.) was added portionwise to a stirred solution of the title compound from Preparative Example 73A, 5
Step D (2.86 g, 13.0 mmol) and *t*-butanol (1.5 mL, 1.2 eq.) in a mixture of liquefied ammonia (125 mL) and anhydrous THF (125 mL) at -60 °C under a nitrogen atmosphere. The dark-blue mixture was slowly (12h) warmed to room temperature and the volatiles were removed under house vacuum at 30 °C. The residue was 10
taken up in distilled water (50 mL) and extracted with diethyl ether (5 x 50 mL). The ethereal extracts were discarded and the aqueous layer was concentrated under house vacuum at 50 °C to give the title compound (1.70 g, 100% crude yield): [M + H]⁺: 130; HRMS (FAB⁺): Calculated for C₇H₁₆NO ([M + H]⁺): 130.1232; Observed: 15
130.1231.

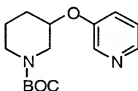
Step F



- By essentially the same procedure set forth in Preparative 20
Example 7, Step C through Step F only substituting the title compound from Preparative Example 73A, Step F, the title compound was prepared.

PREPARATIVE EXAMPLE 74A

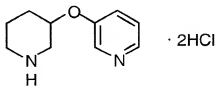
- 25 Step A



- 198 -

Di-isopropyl azodicarboxylate (0.54 mL, 1.5eq.) was added to N-t-butoxycarbonylpiperidin-3-ol (0.37, 1.83 mmol), 3-hydroxypyridine (0.26g, 1.5eq.), and PPh3 (0.72g, 1.5 eq.) in THF (5.0 mL). The resulting solution was stirred at room temperature overnight, concentrated *in vacuo*, and purified by flash chromatography using a 30% hexanes in EtOAc solution as eluent (0.14g, 27% yield): LCMS: MH^+ =279.

Step B

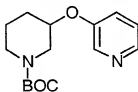


By essentially the same procedure set forth in Preparative Example 8, the title compound was prepared.

PREPARATIVE EXAMPLES 74B AND 74C

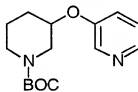
The title compound from Preparative Example 74A was separated into individual C-3 isomers by Preparative HPLC using a CHIRALPAK AD column using a 20% iPrOH in hexanes with 0.2% DEA as eluent.

PREPARATIVE EXAMPLE 74A



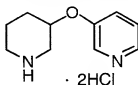
First eluting isomer: LCMS: MH^+ =279.

PREPARATIVE EXAMPLE 74B



Second eluting isomer: LCMS: MH^+ =279.

- 199 -
PREPARATIVE EXAMPLE 74C



By essentially the same procedure set forth in Preparative Example 8 only substituting the title compound from Preparative Example 74A, the title compound was prepared.

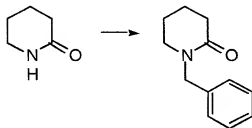
By essentially the same procedure as set forth in Preparative Example 74A, the title compounds in Column 4 of Table 16 were prepared using the 3-hydroxypyridine derivative in Column 2 of Table 16.

TABLE 16

Prep. Ex.	Column 2	Column 3	Column 4
75A			
76			

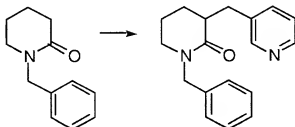
PREPARATIVE EXAMPLE 77

15 Step A



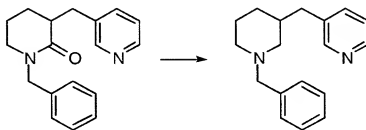
By essentially the same procedure set forth in Preparative Example 73A, Step A, the title compound was prepared: LCMS: $MH^+=190$.

5 Step B



- To a solution of the title compound from Preparative Example 77, Step A (3.68g, 2.4eq.) in THF (50 mL) was added LiHMDS (19.4 mL, 2.4 eq., 1M solution in THF) at -78°C . The resulting solution
- 10 was stirred at -78°C for 2.5 hours before adding 3-bromomethylpyridine hydrobromide (1.39g, 8.09 mmol). The reaction mixture was warmed slowly to room temperature and stirred overnight. The resulting solution was diluted with saturated NH_4Cl (20 mL), extracted with CH_2Cl_2 (3 X 75 mL), dried over
- 15 Na_2SO_4 , filtered and concentrated to give a yellow oil (0.63g, 28% yield): LCMS: $MH^+=281$.

Step C

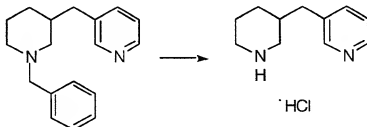


- To a solution of the title compound from Preparative Example 77, Step B (0.65g, 2.31 mmol) in THF (3.0 mL) was added LAH (2.54 mL, 1M in Et_2O) and the resulting solution stirred at room temperature overnight. The reaction mixture was quenched by the addition of saturated Na_2SO_4 , filtered through Celite and
- 25 concentrated under reduced pressure. The product was purified by

- 201 -

flash chromatography using a 20% hexanes in EtOAc solution as eluent a give a yellow oil (0.42g, 68% yield): LCMS: MH⁺=267.

Step D



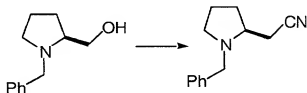
5

The title compound from Preparative Example 77, Step C (0.40g, 1.50 mmol) in dichloroethane (3 mL) was treated with 1-chloroethylchloroformate (0.37 mL, 2.3 eq.). The resulting solution was stirred 3 hours, concentrated under reduced pressure, diluted with MeOH, and heated at reflux for 3 hours. The reaction mixture was cooled, concentrated under reduced pressure, and purified by flash chromatography using a 10% (10% NH₄OH in MeOH) in CH₂Cl₂ solution as eluent (0.20g, 63% yield): LCMS: MH⁺=177.

15

PREPARATIVE EXAMPLE 78

STEP A



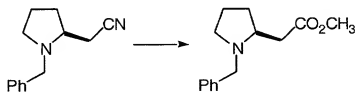
To a solution of (S)-1-benzyl-2-pyrrolidinemethanol (15.5 g, 81.03 mmol) and TEA (16.38 g, 161.93 mmol) in CH₂Cl₂ (200 mL), MsCl (11.13 g, 97.16 mmol) was added at 10 °C and stirred at room temperature overnight. Washed with H₂O and evaporated to dryness to give mesylate (15.6 g) which without further purification, was mixed with NaCN (5.64 g, 115 mmol) and heated at 80° C in DMF (100 mL) overnight. The reaction mixture was evaporated to dryness and extracted with EtOAc, washed with H₂O,

25

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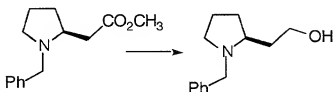
and dried (MgSO_4). The solvent evaporated to give (S)-1-benzyl-2-cyanomethyl-pyrrolidine (11.5 g): (MS, $\text{MH}^+ = 201$).

STEP B



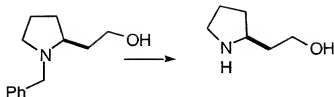
The title compound from Preparative Example 78, Step A (13.0 g) was refluxed in concentrated HCl (100 mL) overnight and evaporated to dryness. The semisolid residue was stirred in MeOH (100 mL), MgSO_4 (5 g) and concentrated H_2SO_4 (2 mL) at 80°C overnight. The reaction mixture was evaporated to dryness to give (S)-1-benzyl-methy-2-pyrrolidineacetate (11.5 g): MS, $\text{MH}^+ = 234$.

STEP C



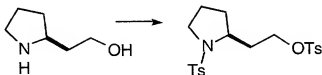
The title compound from Preparative Example 78, Step B (13 g, 55.76 mmol) was dissolved in THF (100 mL) and cooled to 10°C (ice water bath). 1M LAH in ether (111.52 mL, 111.46 mmol) was added slowly and the resulting mixture was refluxed for 2h. The reaction mixture was cooled to room temperature and decomposed with the addition of ice. The residue was extracted with EtOAc and washed with brine and H_2O . The organics were dried and evaporated to a residue which was flash chromatographed on a silica gel column in CH_2Cl_2 / 5% CH_3OH to give (S)-benzyl-hydroxyethyl-pyrrolidine (7.8 g): MS, $\text{MH}^+ = 206$.

STEP D



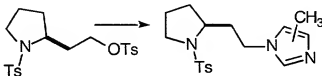
The title compound from Preparative Example 78, Step C (7.7 g) was dissolved in EtOH (80 mL) and hydrogenated over Pd(OH)₂ (2.5 g) at room temperature at 50 psi overnight. The catalyst was filtered and solvent was removed to give (S)-2-hydroxyethylpyrrolidine (4.4 g): MS, MH⁺ = 116.

STEP E



The title compound from Preparative Example 78, Step D (2.4 g, 20.85 mmol) was dissolved in CH₂Cl₂ (250 mL) and cooled to 10 °C. TsCl (11.92 g, 62.52 mmol) followed by TEA (10.54 g, 104.2 mmol) were added and stirred at room temperature overnight. The reaction mixture was diluted with CH₂Cl₂ and washed with brine and H₂O. The organics were dried and solvent evaporated to give (S)-2-(tosyloxyethyl)pyrrolidine (3.96 g): MS, MH⁺ = 332.

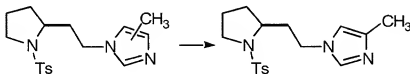
STEP F



The title compound from Preparative Example 78, Step E (3.96 g, 9.2 mmol) was dissolved in DMF (15 mL) and cooled to 10 °C. NaH (0.74 g, 60%, 18.43 mmol) was added slowly and stirred at room temperature until a clear solution was obtained. 4-Methylimidazole (1.51 g, 18.43 mmol) was then added and heated at 80 °C.

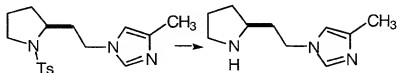
C overnight. The resulting solution was evaporated to dryness and the residue was extracted with CH_2Cl_2 and washed with brine and H_2O . The combined organics were dried and solvent evaporated to give a crude product which was flash chromatographed on a silica
 5 get column in CH_2Cl_2 / 5% (CH_3OH -10% NH_4OH) to give a mixture (S)-tosyl-2- (4 -methyl- 1H-imidazol)-ethyl-1-pyrrolidine (2.98 g, MS, $\text{MH}^+ = 334$) and (S)-tosyl-2- (5 -methyl- 1H-imidazol)-ethyl-1-pyrrolidine (2.98 g): MS, $\text{MH}^+ = 334$.

10 STEP G



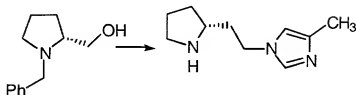
The title compound from 78, Step F (2.9 g) and trityl chloride (1.5 g) were stirred in CH_2Cl_2 (35 mL) at 10°C overnight. The reaction mixture was flash chromatographed on a silica gel column
 15 in acetone /ethyl acetate (1:1) to give (S)-tosyl-2-(4-methyl-1H-imidazol)-ethyl-1-pyrrolidine (0.827 g): (MS, $\text{MH}^+ = 334$).

STEP H



The title compound from Preparative Example 78, Step G (0.82 g) was dissolved in dry THF (2 mL) and liquid ammonia (150 mL). Sodium pieces were added until the blue colour remained and the resulting solution was stirred for 1/2 hr. EtOH was added dropwise until the blue coloured disappeared. The resulting
 25 solution was evaporated to dryness to give sticky white solid which was chromatographed on a flash silica gel column in CH_2Cl_2 / 20% (CH_3OH -10% NH_4OH) to give the title compound (S)-2-(4-methyl-1H-imidazol)-ethyl-1-pyrrolidine, (0.375 g): MS, $\text{MH}^+ = 180$.

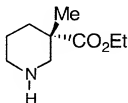
- 205 -
PREPARATIVE EXAMPLE 79



By essentially the same procedure as that set forth in
 Preparative Example 78, (R)-2-(4-methyl-1H-imidazol-1-yl)-
 5 pyrrolidine was prepared from (R)-1-benzyl-2-pyrrolidinemethanol.

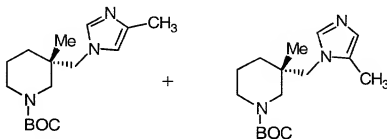
PREPARATIVE EXAMPLE 80

Step A



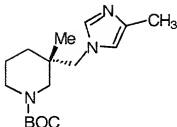
10 The title compound from Preparative Example 68, Step C was
 treated with D-(-)-Tartaric acid and recrystallized from acetone-
 water to afford a piperidine salt enriched in the 3-(S) isomer which
 was neutralized with hydroxide to afford the title compound (11.1 g,
 18%); $MH^+ = 172$.

Step B



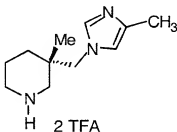
Following the procedures set forth in Preparative Example 7,
 Steps B-E, except using the title compound from Preparative
 20 Example 80, Step A instead of the title compound from Preparative
 Example 7, Step A in Step B, and using 4-methylimidazole and NaH
 instead of sodium imidazole in Step E, the regioisomeric imidazole
 products were obtained (1.1 g, 84%); $MH^+ = 294$.

Step C



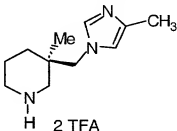
- Following the procedure set forth in Preparative Example 17, except using the title compound from Preparative Example 80, Step B instead of the title compound from Preparative Example 13, the 4-methylimidazole product was obtained (0.501 g, 68%): $MH^+ = 294$.

Step D



- Following the procedure set forth in Preparative Example 68 Step C, except using the title compound from Preparative Example 80 Step C, the amine was obtained as its TFA salt (0.72 g, 100%): $MH^+ = 194$.

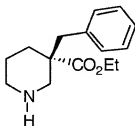
PREPARATIVE EXAMPLE 81



- Following essentially the same procedures set forth in Preparative Example 80, Steps A-D, except using L-(+)-Tartaric acid instead of D-(-)-Tartaric acid in Step A, the amine enriched in the 3- (R) isomer was obtained as its TFA salt (0.157 g, 100%): $MH^+ = 194$.

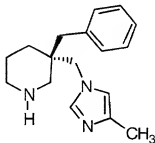
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PREPARATIVE EXAMPLE 82

Step A



- Following essentially the same procedure set forth in
5 Preparative Example 80, Steps A, except using the benzylpiperidine
prepared as described in *J. Med. Chem.* **41**, 2439 (1998) instead of
the title compound from Preparative Example 68, Step C, the amine
enriched in the 3-(S) enantiomer was obtained (6.81 g, 25%): $MH^+ =$
248.

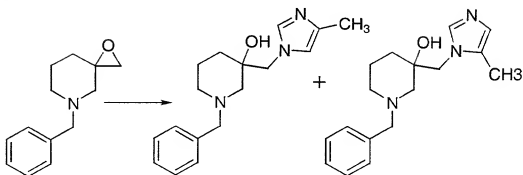
Step B



- Following the procedures set forth in Preparative Example
80, Steps B-D, except using the title compound from Preparative
15 Example 82, Step A instead of the title compound from
Preparative Example 80, Step A in Step B, the 4-methylimidazole
product was obtained as its TFA salt which was neutralized with
NaOH (aq.) to give the amine product (0.163 g, 86%): $MH^+ = 270$.

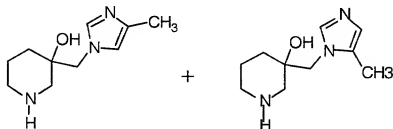
- 208 -
PREPARATIVE EXAMPLE 83

Step A



- 5 The epoxide (*J. Med. Chem.* **30**(1), 1987, pps. 222-225) was treated with 4-methylimidazole and NaH in anhydrous DMF to obtain the resulting mixture of regioisomeric imidazole products (7.77 g, 100%): $MH^+ = 302$.

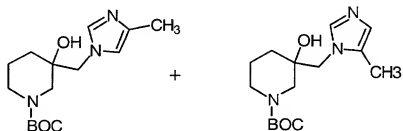
Step B



10

- 15 The product from Preparative Example 83, Step A was treated with H_2 , $Pd(OH)_2/C$ and EtOH in a Parr hydrogenator to afford the amine as a mixture of imidazole regioisomers which were used directly in Step C.

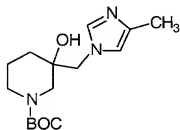
Step C



- 20 Following the procedure set forth in Preparative Example 7, Step C except using the title compound from Preparative Example

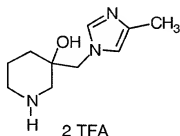
83, Step B instead of the title compound from Preparative Example 7, Step B the BOC derivatives of the regioisomeric methylimidazole products were obtained (5.4 g, 87%): $MH^+ = 296$.

5 Step D



Following the procedure set forth in Preparative Example 17, except using the title compound from Preparative Example 83, Step C instead of the title compound from Preparative Example 13, the
10 4-methylimidazole products were obtained as an enantiomeric mixture (1.03 g, 43%): $MH^+ = 296$.

Step E



15 Following the procedure set forth in Preparative Example 68, Step C except using the title compound from Preparative Example 83, Step D the amine was obtained as its TFA salt (6.3 g, 100%): $MH^+ = 197$.

20

PREPARATIVE EXAMPLE 84

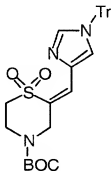
Step A

N-Butoxycarbonyl-[(1-triazolyl-imidazol-5-yl)hydroxymethyl]-4-thiomorpholinyl]carbonyl]-1-piperazinecarboxylate s,s-dioxide

5 mixture and stirred for 20 minutes. 1-N-trityl-imidazole-4-carboxaldehyde (4.62 gm, 13.6 mmol) was dissolved in in 70 ml of THF and added to the reaction mixture. After 4 hours the reaction mixture was poured into sat. NH_4Cl solution and extracted with EtOAc three times. The extracts were combined, dried over MgSO_4 and the solvent evaporated under reduced pressure. The crude mixture was chromatographed on a silica gel column using 1% MeOH/ CH_2Cl_2 to obtain 3.21 gm of title product.

Step B

15 N-Butoxycarbonyl-[(1triazolyl-imidazol-5-yl)methylene]-4-
thiomorpholinyl]carbonyl]-1-piperazinecarboxylate s.s-dioxide

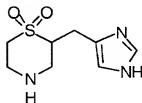


N-Butoxycarbonyl-[(1 triazolyl-imidazol-5-yl)hydroxymethyl]-4-thiomorpholinyl]carbonyl]-1-piperazinecarboxylate s,s-dioxide (2.4 gm) was dissolved in CH_2Cl_2 (48 mL). TEA (1.32 ml) and MsCl (0.4 ml) was added and the reaction mixture stirred under dry nitrogen.

After 24 hours the reaction mixture was added to brine and the product extracted with CH_2Cl_2 to obtain 1.56 gm of title product.

Step C

- 5 N-Butoxycarbonyl-[(1H-imidazol-5-yl)methyl]-4-thiomorpholinyl]carbonyl]-1-piperazinecarboxylate s,s-dioxide

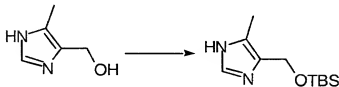


- 10 N-Butoxycarbonyl-[(1 triazolyl-imidazol-5-yl)methylene]-4-thiomorpholinyl]carbonyl]-1-piperazinecarboxylate s,s-dioxide (0.68 gm) was dissolved in EtOH. 10% Pd/C (0.1g) was added and the mixture hydrogenated under balloon H_2 conditions for 24 hours. The catalyst was filtered and the filtrate evaporated to obtain 0.3g of a mixture which was then treated with 1N HCl/ Et_2O to obtain the HCl salt.

15

PREPARATIVE EXAMPLE 85

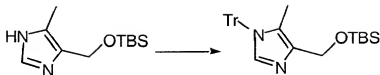
Step A



- 20 4-Hydroxymethyl-5-methylimidazole hydrochloride (4 g, 30 mmol) was dissolved in DMF. TBDMSCl (6.1 g, 45 mmol) and imidazole (5.1 g, 75 mmol) were added and the reaction mixture stirred at ambient temperature for 24 hours. The reaction mixture was poured into water and extracted with EtOAc to obtain 7 gms of title product.

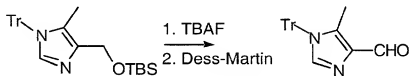
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Step B



4-tert.butyldimethylsilyloxymethyl-5-methyl-imidazole (9 gm, 40 mmol) was dissolved in 100 ml of CH_2Cl_2 . TEA (6 ml) and TrCl (11 gm, 40 mmol) were added and the reaction mixture stirred for six hours. The reaction mixture was added to brine, extracted with EtOAc, and purified on a silica gel column to obtain 7.97 gm of title product as a white solid.

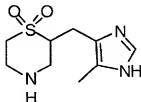
10 Step C



1-trityl-4-tert.butyldimethylsilyloxymethyl-5-methyl-imidazole (7.92 gm, 17 mmol) was dissolved in dry THF and 17ml of 1M TBAF in THF was added. The reaction mixture was stirred at room temperature for 3 hours. 100 ml of H_2O was added and the precipitate was filtered and dried under vacuum to obtain 5.33 gm of title product.

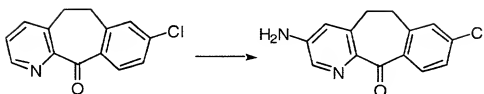
Step D

20 N-Butoxycarbonyl-[(1H-4-methyl-imidazol-5-yl)methylene]-4-thiomorpholinyl carbonyl-1-piperazinecarboxylate s,s-dioxide



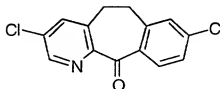
By essentially the same procedure set forth in Preparative Example 84, Step 1 through Step C, the title product was prepared.

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PREPARATIVE EXAMPLE 85A



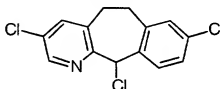
- By essentially the same procedure set forth in Njoroge et. al. (J. Med. Chem. (1997), **40**, 4290) for the preparation of 3-aminoloratadine only substituting the 3-H ketone (J. Het. Chem (1971) **8**, 73) for loratadine, the title compound was prepared.

PREPARATIVE EXAMPLE 86



- The title compound from Preparative Example 85A (1.0g, 3.87 mmol) was added portionwise to t-butyl nitrite (0.69 mL, 1.5 eq.) and CuCl_2 (0.62g, 1.2 eq.) in CH_3CN (20 mL) at 0°C . The resulting solution was warmed slowly to room temperature and stirred 72 hours. The reaction mixture was quenched with 1N HCl (10 mL), neutralized with 15% NH_4OH and extracted with EtOAc (3X50 mL). The combined organics were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography using a 50 : 50 EtOAc : hexanes mixture as eluent to give a pale yellow solid (0.72g, 67% yield).
- FABMS: $\text{MH}^+=278$.

PREPARATIVE EXAMPLE 87

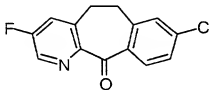


- The title compound from Preparative Example 85A (0.72g, 2.59 mmol) was dissolved in THF (10 mL) and treated with NaBH_4

(0.13g, 1.3 eq.). The resulting solution was stirred at room temperature 1 hour. The reaction mixture was quenched by the addition of 1N NaOH and the resulting solution extracted with EtOAc (3 X 50 mL). The combined organics were dried over Na₂SO₄,
5 filtered, and concentrated under reduced pressure to give a tan solid which was used without further purification (0.71g, 97% crude yield). The crude product was dissolved in toluene (15 mL), cooled to 0 °C, and treated with SOCl₂ (0.32 mL, 1.75 eq.). The resulting solution was stirred at 0 °C for 1 hour and room temperature for 2
10 additional hours. The reaction mixture was diluted with CH₂Cl₂ (30 mL) and washed with 1N NaOH (20 mL) and the organic layer dried over Na₂SO₄, filtered, concentrated, and used without further purification (0.76g, 100 crude yield).

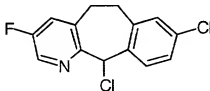
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PREPARATIVE EXAMPLE 88



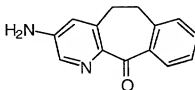
The title compound from Preparative Example 85A (1.62g, 6.26 mmol) was added portionwise to NO⁺BF₄⁻ (0.81g, 1.1 eq.) in toluene (10 mL) at 0 °C. The resulting slurry was stirred at 0 °C for
20 2.5 hours before warming to room temperature. The reaction mixture was heated at reflux for 2 hours, cooled, neutralized with 1N NaOH and extracted with EtOAc (3 X 50 mL). The combined organics were washed with 1N HCl (2 X 25 mL), saturated NaHCO₃ (1 X 25 mL), and water (1 X 15 mL), dried over Na₂SO₄, filtered, and
25 concentrated under reduced pressure. The crude product was purified by flash chromatography using a 70 : 30 hexanes : EtOAc mix as eluent to yield a yellow solid (0.68g, 42% yield). LCMS: MH⁺=262.

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PREPARATIVE EXAMPLE 89



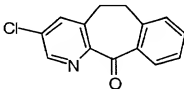
By essentially the same procedure set forth in Preparative Example 87, the title compound was prepared and used without
5 further purification (0.66g, 100% crude yield).

PREPARATIVE EXAMPLE 90



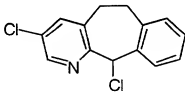
10 NH_4HCO_2 (2.44g, 10eq.) was added to a solution of the title compound from Preparative Example 73A (2.00g, 7.74 mmol) and 5% Pd/C (0.50g) in EtOH (100 mL) and the resulting solution was heated to reflux 2 hours. The reaction mixture was cooled, filtered through a plug of Celite and concentrated under reduced pressure. The residue was diluted with H_2O (100 mL) and extracted with
15 CH_2Cl_2 (3 x 75 mL). The combined organics were dried over Na_2SO_4 , filtered, and concentrated in vacuo to give a yellow solid (1.22g, 70% yield) which was used without further purification: FABMS: MH^+ = 225.

20 PREPARATIVE EXAMPLE 91



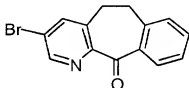
By essentially the same procedure set forth in Preparative Example 86, the title compound was prepared (0.81g, 61%
yield):FABMS: MH^+ = 244.

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PREPARATIVE EXAMPLE 92



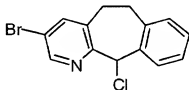
By essentially the same procedure set forth in Preparative
Example 87, the title compound was prepared and used without
5 further purification.

PREPARATIVE EXAMPLE 92A



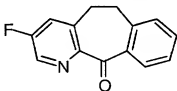
By essentially the same procedure set forth in Preparative
10 Example 86, only substituting CuBr_2 for CuCl_2 the title compound
was prepared (1.33g, 60% yield):FABMS: $\text{MH}^+ = 244$.

PREPARATIVE EXAMPLE 93



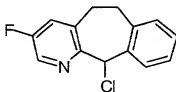
15 By essentially the same procedure set forth in Preparative
Example 87, the title compound was prepared and used without
further purification.

PREPARATIVE EXAMPLE 94



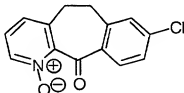
20 By essentially the same procedure set forth in Preparative
Example 88 only substituting the title compound from Preparative
Example 90, the title compound was prepared. FABMS: $\text{MH}^+ = 228$.

PREPARATIVE EXAMPLE 95



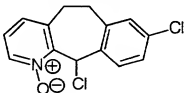
By essentially the same procedure set forth in Preparative
5 Example 87, the title compound was prepared.

PREPARATIVE EXAMPLE 96



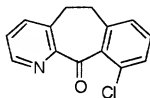
A solution of 3-peroxybenzoic acid (25 g, 2.5 eq.) in
10 anhydrous dichloromethane (250 mL) was added dropwise over a
period of one hour to a stirred solution of 8-chloro-4-aza-10,11-
dihydro-5H-dibenzo[a,d]cyclohepten-5-one (10 g, 41.04 mmol) in
anhydrous CH_2Cl_2 (100 mL) at 0 °C under a nitrogen atmosphere.
The solution was slowly (3h) warmed to room temperature and
15 stirred for another 12h. The solution was extracted with 1 M NaOH
(5 x 100 mL), washed with brine (2 x 100 mL), dried over Na_2SO_4 ,
filtered, and concentrated under house vacuum at 30 °C to give a
canary-yellow solid which was used without purification (10 g, 94%
yield): $[\text{M} + \text{H}]^+$: 260; HRMS (FAB+): Calculated for $\text{C}_{14}\text{H}_{11}\text{ClNO}_2$ ($[\text{M} +$
20 $\text{H}]^+$): 260.0475 Observed: 260.0478.

PREPARATIVE EXAMPLE 97



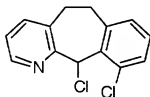
By essentially the same procedure set forth in Preparative
25 Example 87, the title compound was prepared (9.55g, 99% yield).

PREPARATIVE EXAMPLE 98



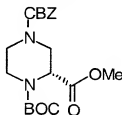
The title compound was prepared according to the methods
5 described in U.S. Patent No. 3,419,565.

PREPARATIVE EXAMPLE 99



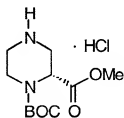
By essentially the same procedure set forth in Preparative
10 Example 87, the title compound was prepared (2.4g, 87% yield).

PREPARATIVE EXAMPLE 100



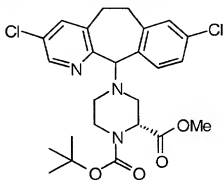
MeI (1.75 mL, 3.0 eq.) added to a solution of Cs_2CO_3 (9.12g,
15 3.0 eq.) and the title compound from Preparative Example 4 (3.40g,
9.33 mmol) in DMF (10 mL). The resulting solution was stirred at
room temperature 4 hours. The reaction mixture was concentrated
under reduced pressure, diluted with H_2O (50 mL) and extracted
with CH_2Cl_2 (3 X 50 mL). The combined organics were dried over
20 Na_2SO_4 , filtered, and concentrated *in vacuo*. The crude product was
purified using a 50 : 50 EtOAc : hexanes mix as eluent (1.4g, 40%
yield). FABMS: $\text{MH}^+ = 379$.

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Preparative Example 101



A solution of the title compound from Preparative Example 100 (1.40g, 3.70 mmol) and 5% Pd/C (0.50g) in MeOH (20 mL) and 1N HCl (5 mL) was stirred under 1 atm of H₂ overnight. The reaction mixture was filtered through a plug of Celite and concentrated *in vacuo* to give a white solid (1.02g, 98% yield) which was used without purification. FABMS: MH⁺=245.

PREPARATIVE EXAMPLE 102



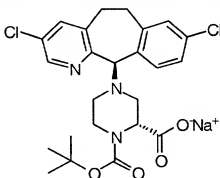
A solution of the title compound from Preparative Example 101 (1.01g, 3.78 mmol) and TEA (2.63 mL, 5 eq.) in DMF (10 mL) were stirred at room temperature for 30 minutes before adding the title compound from Preparative Example 87 (1.68g, 1.5eq.). The resulting solution was stirred at room temperature overnight and concentrated under reduced pressure. The residue was diluted with saturated NaHCO₃ (25 mL) and extracted with CH₂Cl₂ (3 X 50 mL). The combined organics were dried over Na₂SO₄, filtered, and concentrated and the crude product purified by flash chromatography using a 3% EtOAc in CH₂Cl₂ solution as eluent to give an off-white solid (1.1g, 39% yield); LCMS: MH⁺=506.

The individual C-11 (R)- and (S)-isomers were separated by Preparative HPLC using a CHIRALPAK AD column using a 15% iPrOH in hexanes with 0.2% DEA solution as eluent.

11-(R)-isomer (first eluting isomer): FABMS: $MH^+ = 506$; $[\alpha]_D = +70^\circ$ (5.0 mg in 2.0 mL MeOH).

11-(S)-isomer (second eluting isomer): FABMS: $MH^+ = 506$; $[\alpha]_D = -28^\circ$ (28 mg in 2.0 mL MeOH).

PREPARATIVE EXAMPLE 103



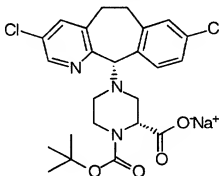
10

A solution of the title compound (C-11 (R)-isomer) from Preparative Example 102 (0.465g, 0.918 mmol) and 1N NaOH (2.76 mL, 3.0 eq.) in MeOH (15 mL) was heated at reflux 2 hours. The reaction mixture was cooled, concentrated, diluted with EtOAc (25 mL) and washed with brine (10 mL). The organics were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give a white solid (0.45g, 96% yield): FABMS: $MH^+ = 492$; $[\alpha]_D = +57.4^\circ$ (5.0 mg in 2.0 mL MeOH).

15

20

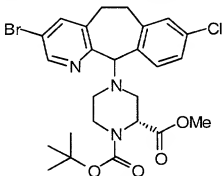
PREPARATIVE EXAMPLE 104



By essentially the same procedure set forth in Preparative Example 103, the title compound (C-11 (S)-isomer) was prepared (0.45g, 96% yield): FABMS: $MH^+ = 492$; $[\alpha]_D = +13.7^\circ$ (5.0 mg in 2.0 mL MeOH).

5

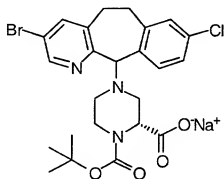
PREPARATIVE EXAMPLE 105



By essentially the same procedure set forth in Preparative Example 102, the title compound (C-11 (R)- and (S)-isomers) was prepared only the C-11 (R)- and (S)-isomers were separated by flash chromatography using a 3% EtOAc in CH_2Cl_2 solution as eluent.

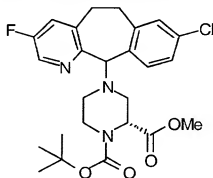
10

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PREPARATIVE EXAMPLE 106



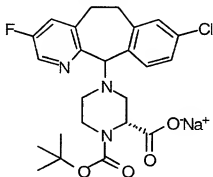
- By essentially the same procedure set forth in
- 5 Preparative Example 103, the title compounds (individual C-11 (R)- and (S)-isomers) were prepared.

PREPARATIVE EXAMPLE 107



- 10 By essentially the same procedure set forth in Preparative Example 102 only substituting the title compound from Preparative Example 89, the title compound was prepared (C-11 (R)- and (S)-isomers) (0.71g, 57% yield): FABMS: $MH^+ = 490$.

PREPARATIVE EXAMPLE 108



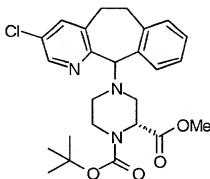
By essentially the same procedure set forth in Preparative Example 103, only using the title compounds (C-11 (R)- and (S)-isomers) from Preparative Example 107, the title compound were prepared. The individual C-11 (R)- and (S)-isomers were separated by flash chromatography using a 12% (10% NH_4OH in MeOH) solution in CH_2Cl_2 as eluent:

C-11 (S)-isomer (first eluting isomer): FABMS: $\text{MH}^+ = 476$.

C-11 (R)-isomer (second eluting isomer): FABMS: $\text{MH}^+ = 476$.

10

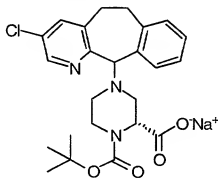
PREPARATIVE EXAMPLE 109



By essentially the same procedure set forth in Preparative Example 102, only substituting the 3-Cl, 8-H title compound from Preparative Example 92 for the 3-Cl, 8-Cl title compound from Preparative Example 101, the title compound (individual C-11 (R)- and C-11 (S)-isomers) was prepared. LCMS: $\text{MH}^+ = 479$.

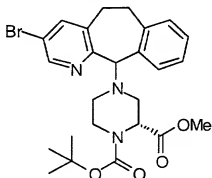
15

PREPARATIVE EXAMPLE 110

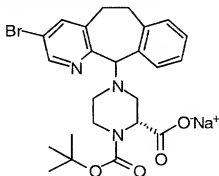


20

By essentially the same procedure set forth in Preparative Example 103, the title compound (individual C-11 (R)- and C-11 (S)-isomers) was prepared. LCMS $\text{MH}^+ = 458$.

PREPARATIVE EXAMPLE 111

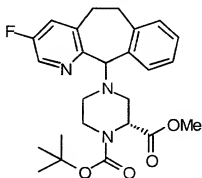
- By essentially the same procedure set forth in Preparative Example 102, only substituting the 3-Br, 8-H title compound from Preparative Example 93 for the 3-Cl, 8-Cl title compound from Preparative Example 101, the title compound (individual C-11 (R)- and C-11 (S)-isomers) was prepared.

PREPARATIVE EXAMPLE 112

10

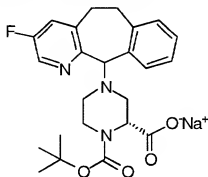
- By essentially the same procedure set forth in Preparative Example 103, the title compound (individual C-11 (R)- and C-11 (S)-isomers) was prepared.

15

PREPARATIVE EXAMPLE 113

By essentially the same procedure set forth in Preparative Example 102, only substituting the 3-F, 8-H title compound from Preparative Example 95 for the 3-Cl, 8-Cl title compound from Preparative Example 101, the title compound (individual C-11 (R)- and C-11 (S)-isomers) can be prepared.

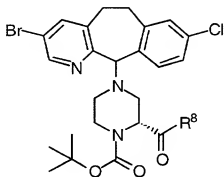
PREPARATIVE EXAMPLE 114



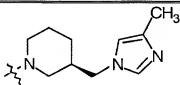
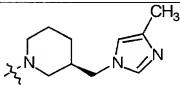
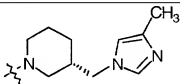
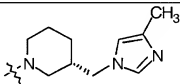
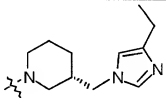
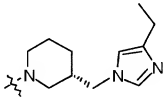
By essentially the same procedure set forth in Preparative Example 103, the title compound (individual C-11 (R)- and C-11 (S)-isomers) can be prepared.

EXAMPLES 138A-168

By essentially the same procedure set forth in Example 1 only substituting the title compounds from Preparative Example 106 (individual (R)- and (S)-isomers) and substituting the appropriate amine, the compounds of the formula shown below with R⁸ listed in column 3 of Table 17 were obtained.

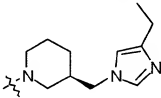
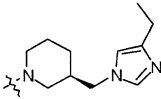
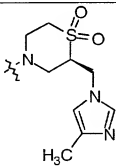
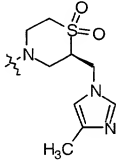


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TABLE 17

Ex.	C-11 isomer	R ⁸ =	MP (°C)	CPD
138A	S		131-135	FABMS: MH ⁺ =697
139A	R		120-126	FABMS: MH ⁺ =697
140A	S		114-121	FABMS: MH ⁺ =697
141A	R		122-126	FABMS: MH ⁺ =697
142A	R		125-127	MS: MH ⁺ = 712
143A	S		109-112	MS: MH ⁺ = 712

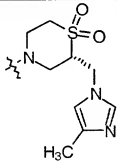
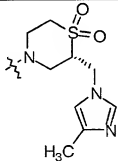
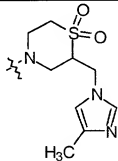
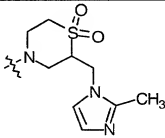
10028251-122001

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TABLE 17 - continued

Ex.	C-11 isomer	R ⁹ =	MP (°C)	CMPD
144A	R		68-71	MS: MH ⁺ = 712
145A	S		97-100	MS: MH ⁺ = 712
146A	S		---	FABMS: MH ⁺ =749
147A	R		---	FABMS: MH ⁺ =749

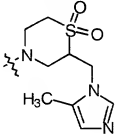
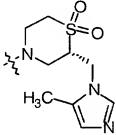
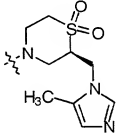
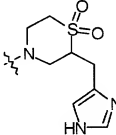
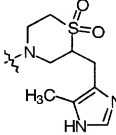
10028251-12001

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TABLE 17 - continued

Ex.	C-11 isomer	R ⁸ =	MP (°C)	COMPD
148	S		---	FABMS: MH ⁺ =749
149	R		---	FABMS: MH ⁺ =749
150	R		---	FABMS: MH ⁺ =749
151	S		---	FABMS: MH ⁺ =749

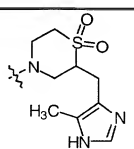
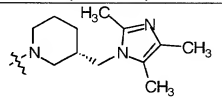
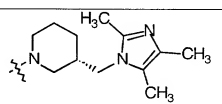
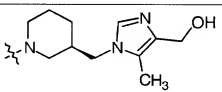
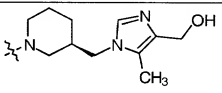
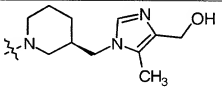
100221-15282001

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TABLE 17 - continued

Ex.	C-11 isomer	R ⁸ =	MP (°C)	CMPD
152	S		---	FABMS: MH ⁺ =749
153	S		---	FABMS: MH ⁺ =749
154	S		---	FABMS: MH ⁺ =749
155	S		---	FABMS: MH ⁺ =735
156	S	 (Isomer 1)	---	---

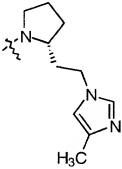
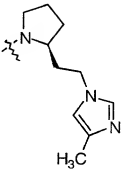
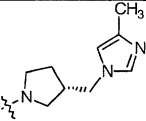
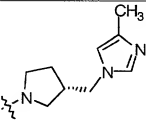
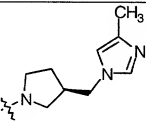
1008251-12001

TABLE 17 - continued

Ex.	C-11 isomer	R ⁸ =	MP (°C)	CMPD
157	S	 <p>(Isomer 2)</p>	---	---
158	R		---	FABMS: MH ⁺ =727
159	S		---	FABMS: MH ⁺ =727
160	R,S		---	FABMS: MH ⁺ =729
161	1		---	FABMS: MH ⁺ =729
162	2		---	FABMS: MH ⁺ =729

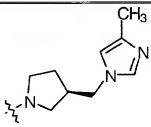
10028251.12001

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TABLE 17 - continued

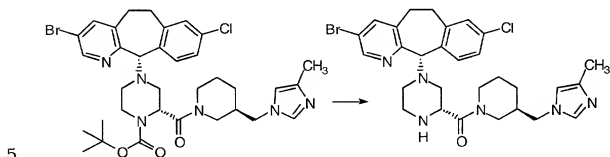
Ex.	C-11 isomer	R ⁹ =	MP (°C)	COMPD
163	S		---	FABMS: MH ⁺ =699
164	S		----	FABMS: MH ⁺ =699
165	S		---	FABMS: MH ⁺ =685
166	R		---	FABMS: MH ⁺ =685
167	S		---	FABMS: MH ⁺ =685

100221-15282001

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TABLE 17 - continued

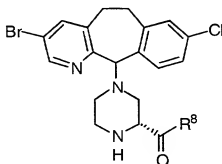
Ex.	C-11 isomer	R ⁸ =	MP (°C)	CPD
168	R		---	FABMS: MH ⁺ =685

PREPARATIVE EXAMPLE 115

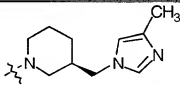
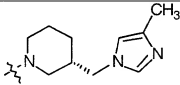
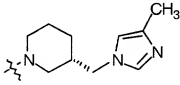


By essentially the same procedure set forth in Preparative Example 24 only using the title compound from Example 73A, the title compound was prepared: FABMS: MH⁺= 599.

10 By essentially the same procedure set forth in Preparative Example 115 only substituting the title compounds from the example listed in column 2, the title compounds of formula shown below with R⁸ as listed in column 4 of Table 18 can be obtained.

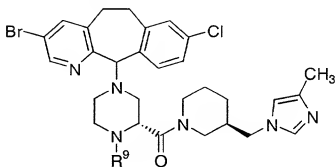


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TABLE 18



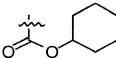
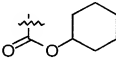
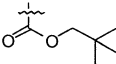
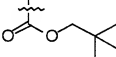
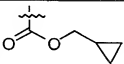
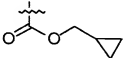

Prep Ex.	Ex.	C-11 isomer	R ⁸ =
116	139A	R	
117	140A	S	
118	141A	R	

EXAMPLES 169-182

- 5 By essentially the same procedure set forth in Example 14,
only substituting the title compounds from the Preparative Example
listed in column 2 of Table 19, the compounds of the formula shown
below with R⁹ as listed in Column 4 of Table 19, were obtained
(where data is provided) or can be obtained (where no data is
10 provided) by using the appropriate electrophile.



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TABLE 19

Ex.	Prep. Ex.	C-11 isomer	R ⁶ =	MP (°C)	CMPD
169	116	R		123- 127	LCMS:MH ⁺ = 683
170	115	S		117- 123	FABMS: MH ⁺ =683
171	116	R		78-83	LCMS: MH ⁺ =723
172	115	S		129- 135	FABMS: MH ⁺ =723
173	116	R		129- 132	LCMS: MH ⁺ =711
174	115	S		121- 125	LCMS: MH ⁺ =711
175	116	R		108- 113	LCMS: MH ⁺ =694
176	115	S		101- 111	LCMS: MH ⁺ =694
177	116	R		148- 151	LCMS: MH ⁺ =696

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TABLE 19 - continued

Ex.	Prep. Ex.	C-11 isomer	R ⁹ =	MP (°C)	CPMPD
178	115	S		149- 154	FABMS: MH ⁺ =696
179	116	R		129- 133	LCMS: MH ⁺ =681
180	115	S		119- 123	FABMS: MH ⁺ =681
181	116	R		---	---
182	115	S		---	---

EXAMPLES 183-196

- 5 By essentially the same procedure set forth in Example 14,
only substituting the title compounds from the Preparative Example
listed in column 2 of Table 20, the compounds of the formula shown
below, with R⁹ as listed in Column 4 of Table 20 were obtained
(where data is provided) or can be obtained (where data is not
10 provided) by using the appropriate electrophile.

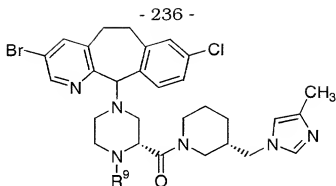
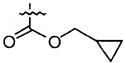
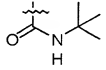
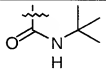


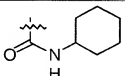
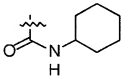


TABLE 20

Ex.	Prep. Ex.	C-11 isomer	R ⁹ =	MP (°C)	CMPD
183	118	R		115- 118	FABMS: MH ⁺ =683
184	117	S		109- 130	LCMS: MH ⁺ =683
185	118	R		82- 85	FABMS: MH ⁺ =723
186	117	S		101- 116	LCMS: MH ⁺ =723
187	118	R		122- 126	LCMS: MH ⁺ =711
188	117	S		128- 131	FABMS: MH ⁺ =711
189	118	R		111- 116	LCMS: MH ⁺ =695

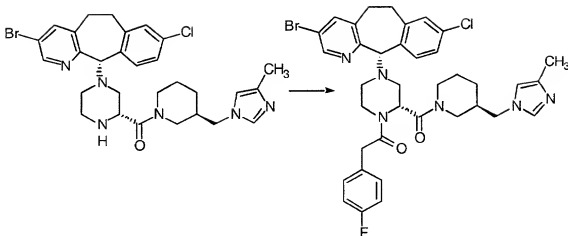
10028251.122001

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TABLE 20 - continued

Ex.	Prep. Ex.	C-11 isomer	R ⁹ =	MP (°C)	CMPD
190	117	S		90- 94	LCMS: MH ⁺ =695
191	118	R		149- 152	FABMS: MH ⁺ =696
192	117	S		110- 135	LCMS: MH ⁺ =696
193	118	R		129- 133	LCMS: MH ⁺ =681
194	117	S		132- 143	LCMS: MH ⁺ =681
195	118	R		---	---
196	117	S		---	---

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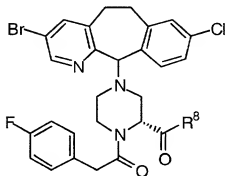
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EXAMPLE 197



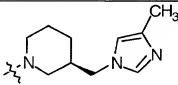
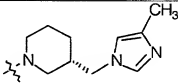
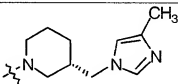
A solution of the title compound from Preparative Example 115 (0.10g, 0.17 mmol) in CH_2Cl_2 (5.0 mL) was treated with p-
5 fluorophenylacetic acid (0.034g, 1.3 eq.), NMM (0.11 mL, 6.0 eq.), HOBT (0.029g, 1.3 eq.), and DEC (0.042g, 1.3 eq.) and the resulting solution was stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo* and the crude product purified by flash chromatography using a 5% (10% NH_4OH in MeOH) solution
10 in CH_2Cl_2 as eluent (0.066g, 53% yield): mp = 105-110 °C; LCMS: $\text{MH}^+ = 733$.

EXAMPLES 198-200

By essentially the same procedure set forth in Example 197,
15 only using the title compounds from the Preparative Example listed in column 2 of Table 21, the title compounds of the formula shown below, with R^8 as listed in column 4 of Table 21, were obtained.

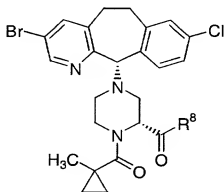


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TABLE 21

Ex.	Prep. Ex.	C-11 isomer	R ⁸ =	MP (°C)	CMPD
198	116	R		134-136	LCMS: MH ⁺ =733
199	117	S		88-92	LCMS: MH ⁺ =733
200	118	R		129-131	LCMS: MH ⁺ =733

EXAMPLES 201-204

- 5 By essentially the same procedure set forth in Example 197, only substituting cyclopropylmethylacetic acid in place of p-fluorophenylacetic acid, and using the title compounds from the Preparative Example listed in column 2 of Table 22, the title compounds of the formula shown below, with R⁸ as listed in column
- 10 4 of Table 22, were obtained (Examples 201 and 203) or can be obtained (Examples 202 and 204).

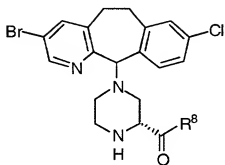


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TABLE 22

Ex.	Prep. Ex.	C-11 isomer	R ⁸ =	MP (°C)	CMPD
201	115	S		135- 137	LCMS: MH ⁺ =679
202	27	R		---	---
203	28	S		135- 139	LCMS: MH ⁺ =679
204	29	R		---	---

PREPARATIVE EXAMPLES 119-134

- 5 By essentially the same procedure set forth in Preparative Example 115, only substituting the title compounds from the example listed in column 2 of Table 23, the title compounds of the formula shown below, with R⁸ as listed in column 4 of Table 23 were obtained.

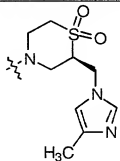
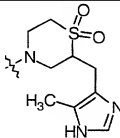
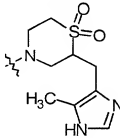
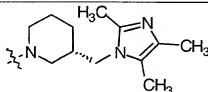
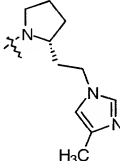


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TABLE 23

Prep Ex.	Ex.	C-11 isomer	R ⁸ =
119	145A	S	
120	144A	R	
121	143A	S	
122	142A	R	
123	150	R	
124	149	S	

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TABLE 23 - continued

Prep Ex.	Ex.	C-11 isomer	R ⁸ =
125	146A	S	
126	156	S	 <p>(Isomer 1)</p>
127	157	S	 <p>(Isomer 2)</p>
128	159	S	
129	163	S	

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TABLE 23 - continued

Prep Ex.	Ex.	C-11 isomer	R ⁸ =
130	164	S	
131	165	S	
132	166	R	
133	167	S	
134	168	R	

EXAMPLES 205-214

- 5 By essentially the same procedure set forth in Example 14, only substituting the title compounds from the Preparative Example listed in column 2 of Table 24, the compounds of the formula shown below, with R⁸ as listed in column 4 of Table 24, were obtained.

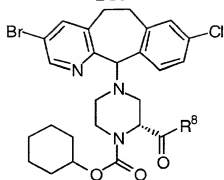
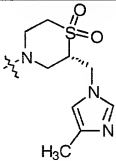
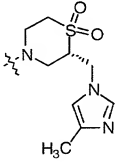
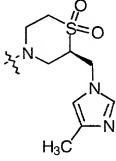
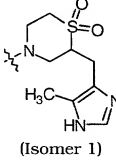


TABLE 24

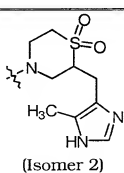
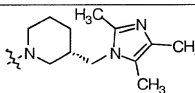
Ex.	Prep. Ex.	C-11 isomer	R ⁸ =	MP (°C)	CMPD
205	122	R		68- 70	MS: MH ⁺ =736
206	121	S		---	---
207	120	R		80- 83	MS: MH ⁺ =736
208	119	S		99- 101	MS: MH ⁺ =736

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TABLE 24 - continued

Ex.	Prep. Ex.	C-11 isomer	R ⁸ =	MP (°C)	COMPD
209	123	R		---	FABMS: MH ⁺ =775
210	124	S		---	FABMS: MH ⁺ =775
211	126	S		---	FABMS: MH ⁺ =775
212	126	S	 (Isomer 1)	---	FABMS: MH ⁺ =775

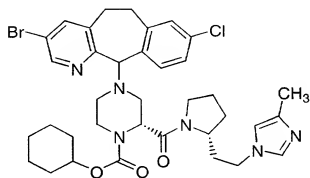
100221.122001

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TABLE 24 - continued

Ex.	Prep. Ex.	C-11 isomer	R ⁹ =	MP (°C)	CPMD
213	127	S	 (Isomer 2)	---	FABMS: MH ⁺ =775
214	128	S		---	FABMS: MH ⁺ =753

EXAMPLE 215

- 5 By essentially the same procedure set forth in Example 14, only substituting the title compound from Preparative Example 129, and using the appropriate electrophile, the compound of formula



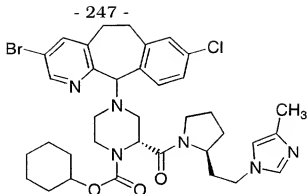
was obtained (C-11 S isomer). FABMS: MH⁺=725.

10

EXAMPLE 216

By essentially the same procedure set forth in Example 14, only substituting the title compound from the Preparative Example 130, and using the appropriate electrophile, the compound of

15 formula



can be obtained (C-11 S isomer). FABMS: $MH^+=725$.

EXAMPLES 217-221

- 5 By essentially the same procedure set forth in Example 14, only substituting the title compounds from the Preparative Example listed in column 2 OF Table 25, the compounds of the formula shown below, with R^9 as listed in column 4 of Table 25, were obtained by using the appropriate electrophile.

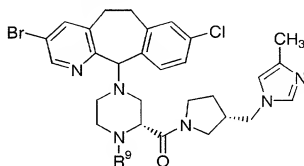

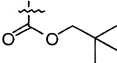
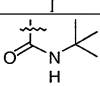


TABLE 25

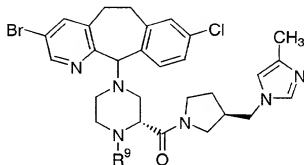
Ex.	Prep. Ex.	C-11 isomer	R^9 =	MP (°C)	CPD
217	131	S		---	FABMS: $MH^+=711$
218	132	R		---	FABMS: $MH^+=711$

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TABLE 25 - continued

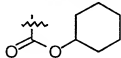
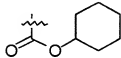
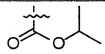
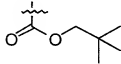
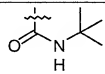
Ex.	Prep. Ex.	C-11 isomer	R ⁹ =	MP (°C)	CPD
219	131	S		---	FABMS: MH ⁺ =671
220	131	S		---	FABMS: MH ⁺ =699
221	131	S		---	FABMS: MH ⁺ =684

EXAMPLES 222-226

- 5 By essentially the same procedure set forth in Example 14, only substituting the title compounds from the Preparative Example listed in column 2 of Table 26, the compounds of the formula shown below, with R⁹ as listed in column 4 of Table 26, were obtained by using the appropriate electrophile.

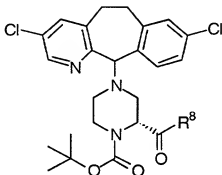


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TABLE 26

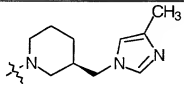
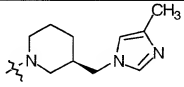
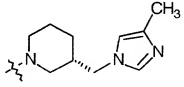
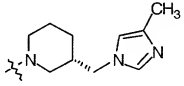
Ex.	Prep. Ex.	C-11 isomer	R ⁸ =	MP (°C)	CMPD
222	133	S		---	FABMS: MH ⁺ =711
223	134	R		---	FABMS: MH ⁺ =711
224	133	S		---	FABMS: MH ⁺ =671
225	133	S		---	FABMS: MH ⁺ =699
226	133	S		---	FABMS: MH ⁺ =684

EXAMPLES 227-230

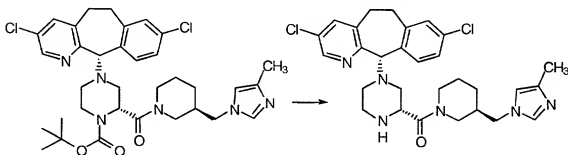
- 5 By essentially the same procedure set forth in Example 1, only substituting the title compounds from Preparative Example 87 and Preparative Example 101, and substituting the appropriate amine, the compounds of the formula shown below with R⁸ listed in column 3 of Table 27 were obtained.



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TABLE 27

Ex.	C-11 isomer	R ⁸ =	MP (°C)	CPD
227	S		100-116	LCMS: MH ⁺ =653
228	R		115-128	LCMS: MH ⁺ =653
229	S		102-113	LCMS: MH ⁺ =653
230	R		121-127	LCMS: MH ⁺ =653

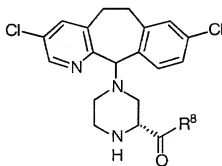
PREPARATIVE EXAMPLE 135



By essentially the same procedure set forth in Preparative Example 24, only using the title compound from Example 227, the title compound was prepared: LCMS: MH⁺=553.

By essentially the same procedure, only substituting the title compounds from the example listed in column 2 of Table 28, the

title compounds of the formula shown below, with R⁸ as listed in column 3 of 28, were obtained.



5

TABLE 28

Prep Ex.	Ex.	C-11 isomer	R ⁸ =
136	228	R	
137	229	S	
138	230	R	

Examples 231-242

- By essentially the same procedure set forth in Example 14, only substituting the title compounds from the Preparative Example listed in column 2 of Table 29, the compounds of the formula shown below, with R⁹ as listed in column 4 of Table 29 were obtained (where data is provided) or can be obtained (were no data is provided) by using the appropriate electrophile.

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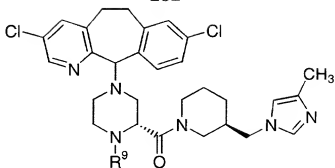
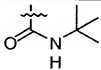
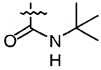


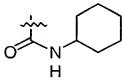
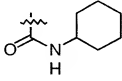


TABLE 29

Ex.	Prep. Ex.	C-11 isomer	R ⁹ =	MP (°C)	CPD
231	136	R		106- 115	LCMS: MH ⁺ =639
232	135	S		92- 101	LCMS: MH ⁺ =639
233	136	R		107- 117	LCMS: MH ⁺ =667
234	135	S		106- 117	LCMS: MH ⁺ =667
235	136	R		---	---
236	135	S		---	---

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TABLE 29 - continued

Ex.	Prep. Ex.	C-11 isomer	R ⁹ =	MP (°C)	CPMD
237	136	R		---	---
238	135	S		107- 113	LCMS: MH ⁺ =652
239	136	R		107- 114	LCMS: MH ⁺ =637
240	135	S		100- 112	LCMS: MH ⁺ =637
241	136	R		---	---
242	135	S		---	---

EXAMPLES 243-254

- 5 By essentially the same procedure set forth in Example 14, only substituting the title compounds from the Preparative Example listed in column 2 of Table 30, the compounds of the formula shown below, with R⁹ as listed in column 4 of Table 30, were obtained (where data is provided) or can be obtained (where no data is
- 10 provided) by using the appropriate electrophile.

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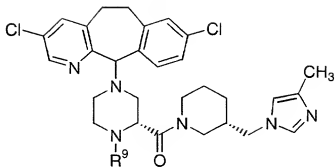




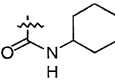
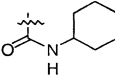


TABLE 30

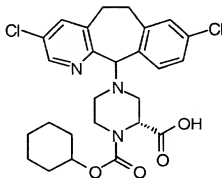
Ex.	Prep. Ex.	C-11 isomer	R ⁹ =	MP (°C)	CPD
243	138	R		103-114	LCMS: MH ⁺ =639
244	137	S		96-106	LCMS: MH ⁺ =639
245	138	R		104-108	LCMS: MH ⁺ =667
246	137	S		100-107	LCMS: MH ⁺ =667
247	138	R		---	---
248	137	S		---	---

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TABLE 30 - continued

Ex.	Prep. Ex.	C-11 isomer	R ⁹ =	MP (°C)	CPMD
249	138	R		---	---
250	137	S		---	---
251	138	R		104-119	LCMS: MH ⁺ =637
252	137	S		100-106	LCMS: MH ⁺ =637
253	138	R		---	---
254	137	S		---	---

PREPARATIVE EXAMPLE 139



By essentially the same procedure set forth in Preparative Example 32 only substituting the 3-Cl, 8-Cl tricyclic chloride prepared in Preparative Example 87 for the 3-H, 8-Cl tricyclic chloride in Step B, the title compound was prepared. FABMS: $MH^+=518$.

PREPARATIVE EXAMPLES 140 and 141

By essentially the same procedure set forth in Example 1, only substituting the appropriate amine, the compounds of the formula shown below, with R^8 as listed in column 3 of Table 31, were obtained.

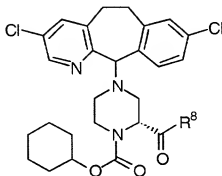
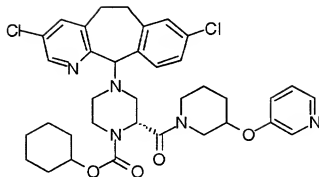


TABLE 31

Prep. Ex.	C-11 isomer	$R^8=$	MP ($^{\circ}C$)	CMPD
140	R,S		---	FABMS: $MH^+=679$
141	R,S		---	LCMS: $MH^+=679$

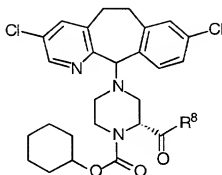
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EXAMPLE 254A



By essentially the same procedure set forth in Example 1 only substituting the title compound from Preparative Example 139 and the amine from Preparative Example 74B, the title compound was prepared. mp=105-113; LCMS: MH⁺=678.

EXAMPLE 255-258

The title compounds from Preparative Examples 140 and 141 were separated into individual C-11 (S)- and (R)-diastereomers by Preparative HPLC with a CHIRALPAK AD column using a 20% iPrOH in hexanes solution with 0.2% DEA as eluent to give the compounds of the formula shown below with R⁸ as listed in Column 3 of Table 32.



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TABLE 32

Ex.	C-11 isomer	R ⁸ =	MP (°C)	CMPD
255	S		116-126	FABMS: MH ⁺ =679 [α] _D =+21.1 (3.62 mg in 2.0 mL MeOH)
256	R		122-128	FABMS: MH ⁺ =679 [α] _D =-20.7 (5.0 mg in 2.0 mL MeOH)
257	S		115-128	LCMS: MH ⁺ =679 [α] _D = +20.1 (5.0 mg in 2.0 mL MeOH)
258	R		115-128	LCMS: MH ⁺ =679 [α] _D = -13.3 (5.0 mg in 2.0 mL MeOH)

EXAMPLES 259-262

- 5 By essentially the same procedure set forth in Example 1, only substituting the title compounds from Preparative Example 89 and Preparative Example 101 and substituting the appropriate amine, the compounds of the formula shown below, with R⁸ listed in column 3 of Table 33 were obtained.

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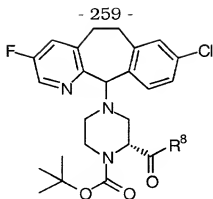
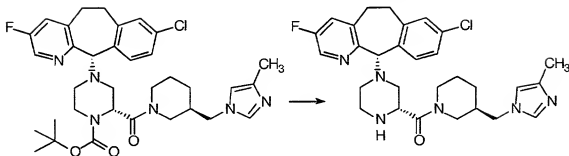


TABLE 33

Ex.	C-11 isomer	R ⁸ =	MP (°C)	CPMD
259	S		126-135	LCMS: MH ⁺ =637
260	R		110-116	FABMS: MH ⁺ =637
261	S		115-118	LCMS: MH ⁺ =637
262	R		122-126	FABMS: MH ⁺ =637

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PREPARATIVE EXAMPLE 142



By essentially the same procedure set forth in Preparative Example 24, only using the title compound from Example 259, the title compound can be prepared.

By essentially the same procedure, only substituting the title compounds from the example listed in column 2 of Table 34, the title compounds of the formula shown below, with R⁸ as listed in column 3 of Table 34, can be prepared.

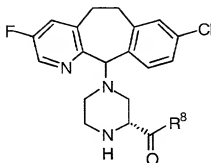


TABLE 34

Prep Ex.	Ex.	C-11 isomer	R ⁸ =
143	260	R	
144	261	S	

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TABLE 34 - continued

Prep Ex.	Ex.	C-11 isomer	R ⁸ =
145	262	R	

EXAMPLES 263-274

- 5 By essentially the same procedure set forth in Example 14, only substituting the title compounds from the Preparative Example listed in column 2 of Table 35, the compounds of the formula shown below, with R⁹ as listed in column 4 of Table 35, were obtained (where data is provided) or can be obtained (where no data is
- 10 provided) by using the appropriate electrophile.

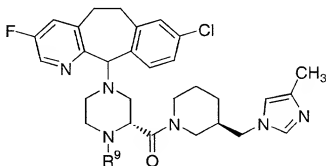
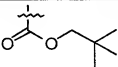
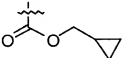
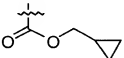
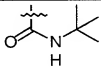
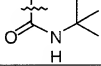


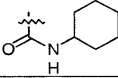
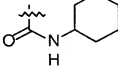


TABLE 35

Ex.	Prep. Ex.	C-11 isomer	R ⁹ =	MP (°C)	CMPD
263	143	R		92-95	LCMS: MH ⁺ =623
264	142	S		103-106	LCMS: MH ⁺ =623
265	143	R		74-81	LCMS: MH ⁺ =651

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TABLE 35 - continued

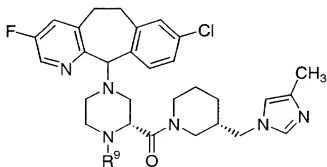
Ex.	Prep. Ex.	C-11 isomer	R ⁹ =	MP [°C]	CMPD
266	142	S		90-95	LCMS: MH ⁺ =651
267	143	R		100- 104	LCMS: MH ⁺ =635
268	142	S		83-87	LCMS: MH ⁺ =635
269	143	R		----	----
270	142	S		----	----
271	143	R		105- 107	LCMS: MH ⁺ =621
272	142	S		75-77	LCMS: MH ⁺ =621
273	143	R		----	----
274	142	S		----	----

EXAMPLES 275-286

5 By essentially the same procedure set forth in Example 14, only substituting the title compounds from the Preparative Example listed in column 2 of Table 36, the compounds of the

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formula shown below, with R⁹ as listed in column 4 of Table 36, can be obtained by using the appropriate electrophile.



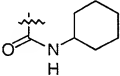
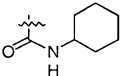


5

TABLE 36

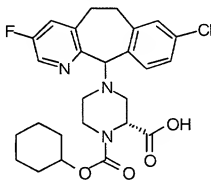
Ex.	Prep. Ex.	C-11 isomer	R ⁹ =
275	145	R	
276	144	S	
277	145	R	
278	144	S	
279	145	R	
280	144	S	
281	145	R	
282	144	S	

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TABLE 36 - continued

Ex.	Prep. Ex.	C-11 isomer	R ^o =
283	145	R	
284	144	S	
285	145	R	
286	144	R	

5

PREPARATIVE EXAMPLE 146 AND 147



By essentially the same procedure set forth in Preparative Example 36, only substituting the 3-F, 8-Cl tricyclic chloride prepared in Preparative Example 89 for the 3-H, 8-Cl tricyclic chloride in Step B, the title compounds (C-11(S)- and (R)-isomers) were prepared and separated into individual diastereomers by flash chromatography using a 12% (10% NH₄OH in MeOH) solution in CH₂Cl₂:

PREPARATIVE EXAMPLE 146

11-(S)-isomer (first eluting isomer): FABMS: $MH^+=502$; $[\alpha]_D=+7.7^\circ$ (5.0 mg in 2 mL MeOH).

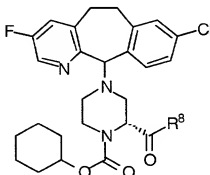
5

PREPARATIVE EXAMPLE 147

11-(R)-isomer (second eluting isomer): FABMS: $MH^+=502$; $[\alpha]_D=+74.6^\circ$ (5.0 mg in 2 mL MeOH).

EXAMPLES 287-290

10 By essentially the same procedure set forth in Example 1, only substituting the title compounds from Preparative Example 132 (individual (S)- and (R)-isomers) and substituting the appropriate amine, the compounds of the formula shown below, with R^8 as listed in Column 3 of Table 37 were obtained.

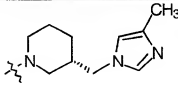
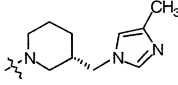


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TABLE 37

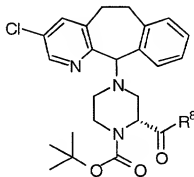
Ex.	C-11 isomer	$R^8=$	MP ($^\circ C$)	CMPD
287	S		116-123	FABMS: $MH^+=663$ $[\alpha]_D=-34.4$ (5.0 mg in 2.0 mL MeOH)
288	R		128-134	FABMS: $MH^+=663$ $[\alpha]_D=+38.6$ (5.0 mg in 2.0 mL MeOH)

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TABLE 37 - continued

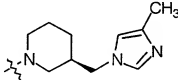
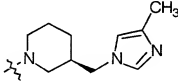
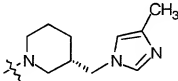
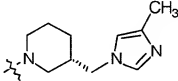
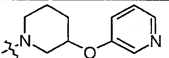
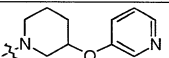
Ex.	C-11 isomer	R ⁸ =	MP (°C)	CMPD
289	S		120-126	FABMS: MH ⁺ =663 [α] _D =-29.4 (5.0 mg in 2.0 mL MeOH)
290	R		121-125	FABMS: MH ⁺ =663 [α] _D =+34.2 (5.0 mg in 2.0 mL MeOH)

EXAMPLES 291-294

- 5 By essentially the same procedure set forth in Example 1, only substituting the title compounds from Preparative Example 110 and substituting the appropriate amine, the compounds of the formula shown below, with R⁸ listed in column 3 of Table 38 were prepared.



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TABLE 38

Ex.	C-11 isomer	R ⁸ =	MP (°C)	CMPD
291	S		99-107	LCMS: MH ⁺ =619
292	R		95-105	LCMS: MH ⁺ =619
293	S		110-123	LCMS: MH ⁺ =619
294	R		102-118	LCMS: MH ⁺ =619
294 A	S		93-107	LCMS: MH ⁺ =618
294 B	R		102-113	LCMS: MH ⁺ =618

PREPARATIVE EXAMPLE 148-151

- 5 By essentially the same procedure set forth in Preparative Example 107, only substituting the title compounds from the example listed in column 2 of Table 39, the title compounds of formula shown below, with R⁸ as listed in column 4 of Table 39, were prepared.

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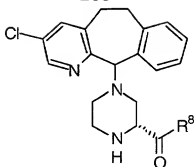


TABLE 39

Prep Ex.	Ex.	C-11 isomer	R ⁸ =	CMPD
148	291	S		LCMS: MH ⁺ =519
149	292	R		LCMS: MH ⁺ =519
150	293	S		LCMS: MH ⁺ =519
151	294	R		LCMS: MH ⁺ =519

5

EXAMPLES 295-306

By essentially the same procedure set forth in Example 14, only substituting the title compounds from the Preparative Example listed in column 2 of Table 40, the compounds of the formula shown below, with R⁹ as listed in column 4 of Table 40, were obtained (where data is provided) or can be obtained (where no data is provided) by using the appropriate electrophile.

10

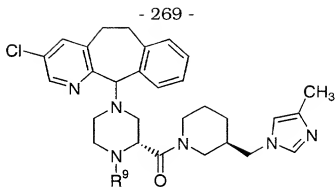




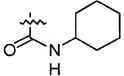
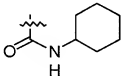


TABLE 40

Ex.	Prep Ex.	C-11 isomer	R ⁹ =	MP (°C)	CMPD
295	149	R		----	----
296	148	S		----	----
297	149	R		94-119	LCMS: MH ⁺ =633
298	148	S		110- 125	LCMS: MH ⁺ =633
299	149	R		95-104	LCMS: MH ⁺ =617
300	148	S		95-101	LCMS: MH ⁺ =617

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TABLE 40 - continued

Ex.	Prep Ex.	C-11 isomer	R ⁹ =	MP (°C)	CPD
301	149	R		107- 119	LCMS: MH ⁺ =618
302	148	S		110- 121	LCMS: MH ⁺ =618
303	149	R		96-119	LCMS: MH ⁺ =603
304	148	S		---	---
305	149	R		---	---
306	148	S		---	---

EXAMPLES 307-318

- 5 By essentially the same procedure set forth in Example 14, only substituting the title compounds from the Preparative Example listed in column 2 of Table 41, the compounds of the formula shown below, with R⁹ as listed in column 4 of Table 41, can be obtained by using the appropriate electrophile.

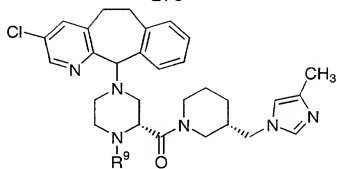


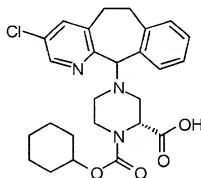
TABLE 41

Ex.	Prep. Ex.	C-11 isomer	R ⁹ =
307	151	R	
308	150	S	
309	151	R	
310	150	S	
311	151	R	
312	150	S	
313	151	R	
314	150	S	
315	151	R	

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TABLE 41 - continued

Ex.	Prep. Ex.	C-11 isomer	R ⁹ =
316	150	S	
317	151	R	
318	150	S	

PREPARATIVE EXAMPLE 152



5

By essentially the same procedure set forth in Preparative Example 36, only substituting the 3-Cl, 8-H tricyclic chloride prepared in Preparative Example 92 for the 3-H, 8-Cl tricyclic chloride in Step B, the title compounds (C-11(S)- and (R)-isomers) was prepared. FABMS: MH⁺ = 484.

10

PREPARATIVE EXAMPLES 153 and 154

By essentially the same procedure set forth in Example 1, only substituting the title compounds from Preparative Example 152 and substituting the appropriate amine, the compounds of the formula shown below, with R⁹ as listed in column 3 of Table 42, were obtained.

15

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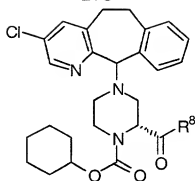


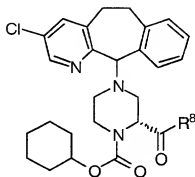
TABLE 42

Prep. Ex.	C-11 isomer	R ⁸ =	CMPD
153	R,S		FABMS: MH ⁺ =645
154	R,S		FABMS: MH ⁺ =645

5

EXAMPLES 319-322

The title compounds from Preparative Examples 153 and 154 were separated into individual C-11 (S)- and (R)-diastereomers by Preparative HPLC with a CHIRALPAK AD column using a 25% iPrOH in hexanes solution with 0.2% DEA as eluent to give the compounds of the formula shown below with R⁸ as listed in column 3 of Table 43.



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TABLE 43

Ex.	C-11 isomer	R ⁸ =	MP (°C)	CMPD
319	S		114-118	FABMS: MH ⁺ =645
320	R		115-120	FABMS: MH ⁺ =645
321	S		112-121	FABMS: MH ⁺ =645
322	R		117-125	FABMS: MH ⁺ =645

EXAMPLES 323-326

- 5 By essentially the same procedure set forth in Example 1, only substituting the title compounds from Preparative Example 112 and substituting the appropriate amine, the compounds of the formula shown below, with R⁸ listed in column 3 of Table 44, can be obtained.

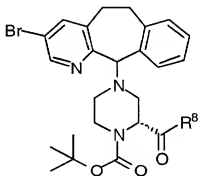
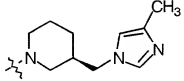
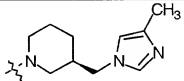
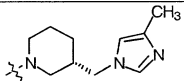
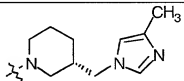


TABLE 44

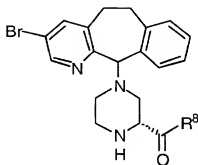
Ex.	C-11 isomer	R ⁸ =	MP (°C)	CMPD
323	S		109-124	LCMS: MH ⁺ =663
324	R		102-119	LCMS: MH ⁺ =663
325	S		---	---
326	R		---	---

5

PREPARATIVE EXAMPLE 155-158

By essentially the same procedure set forth in Preparative Example 115, only substituting the title compounds from the example listed in column 2 of Table 45, the title compounds of the formula shown below, with R⁸ as listed in column 4 of Table 45, can

10 be prepared.

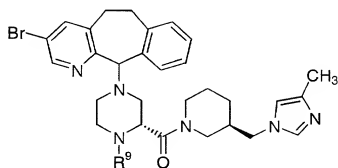


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TABLE 45



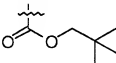
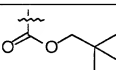
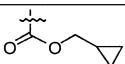
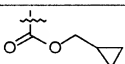



Prep Ex.	Ex.	C-11 isomer	R ⁸ =
155	323	S	
156	324	R	
157	325	S	
158	326	R	

EXAMPLES 327-338

- 5 By essentially the same procedure set forth in Example 14, only substituting the title compounds from the Preparative Example listed in column 2 of Table 46, the compounds of the formula shown below, with R⁹ as listed in column 4 of Table 46, were obtained (where data is provided) or can be obtained (where no data is
- 10 provided) by using the appropriate electrophile.


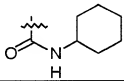
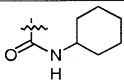


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TABLE 46

Ex.	Prep. Ex.	C-11 isomer	R ⁹ =	MP (°C)	CMPD
327	156	R		----	----
328	155	S		----	----
329	156	R		112- 118	LCMS: MH ⁺ =677
330	155	S		98- 122	LCMS: MH ⁺ =677
331	156	R		93- 103	LCMS: MH ⁺ =661
332	155	S		89- 108	LCMS: MH ⁺ =661
333	156	R		84- 108	LCMS: MH ⁺ =662
334	155	S		91- 118	LCMS: MH ⁺ =662
335	156	R		103- 113	LCMS: MH ⁺ =647

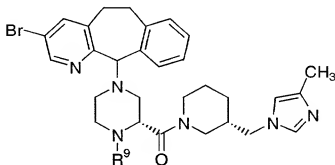
100221-15282001

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TABLE 46 - continued

Ex.	Prep. Ex.	C-11 isomer	R ⁹ =	MP (°C)	CMPD
336	155	S		115- 124	LCMS: MH ⁺ =647
337	156	R		----	----
338	155	S		----	----


EXAMPLES 339-350

- 5 By essentially the same procedure set forth in Example 14, only substituting the title compounds from the Preparative Example listed in column 2 of Table 47, the compounds of the formula shown below with R⁹ as listed in column 4 of Table 47, can be obtained by using the appropriate electrophile.

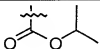
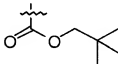
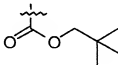
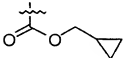
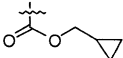
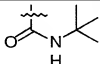
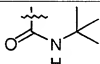


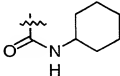
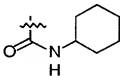


10

TABLE 47

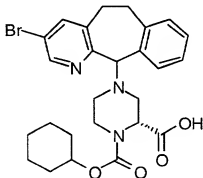
Ex.	Prep. Ex.	C-11 isomer	R ⁹ =
339	158	R	

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TABLE 47 - continued

Ex.	Prep. Ex.	C-11 isomer	R ⁹ =
340	157	S	
341	158	R	
342	157	S	
343	158	R	
344	157	S	
345	158	R	
346	157	S	
347	158	R	
348	157	S	
349	158	R	
350	157	S	

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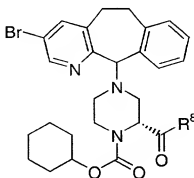
PREPARATIVE EXAMPLE 159



- By essentially the same procedure set forth in Preparative Example 36, only substituting the 3-Br, 8-H tricyclic chloride prepared in Preparative Example 93 for the 3-H, 8-Cl tricyclic chloride in Step B, the title compounds (C-11(S)- and (R)-isomers) were prepared. FABMS: $MH^+ = 528$.

PREPARATIVE EXAMPLES 160 and 161

- By essentially the same procedure set forth in Preparative Example 126, only substituting the title compounds from Preparative Example 144 and substituting the appropriate amine, the compounds of the formula shown below, with R^8 as listed in column 3 of Table 48, were obtained.



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TABLE 48

Prep. Ex.	C-11 isomer	R ⁸ =	CMPD
160	R,S		FABMS: MH ⁺ =689
161	R,S		FABMS: MH ⁺ =689

EXAMPLES 351-354

- 5 The title compounds from Preparative Examples 160 and 161 were separated into individual C-11 (S)- and (R)-diastereomers by Preparative HPLC with a CHIRALPAK AD column using a iPrOH in hexanes solution with 0.2% DEA as eluent to give the compounds of the formula shown below with R⁸ as listed in column 3 of Table 49.

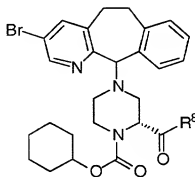


TABLE 49

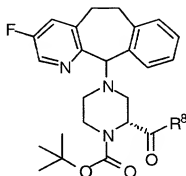
Ex.	C-11 isomer	R ⁸ =	MP (°C)	CMPD
351	S		120- 124	FABMS: MH ⁺ =689

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TABLE 49 - continued

Ex.	C-11 isomer	R ⁸ =	MP (°C)	CPMD
352	R		122-125	FABMS: MH ⁺ =689
353	S		121-127	FABMS: MH ⁺ =689
354	R		124-128	FABMS: MH ⁺ =689

EXAMPLES 355-358

- 5 By essentially the same procedure set forth in Example 1 only substituting the title compounds from Preparative Example 114 and substituting the appropriate amine, the compounds of the formula shown below, with R⁸ listed in column 3 of Table 50, can be obtained.

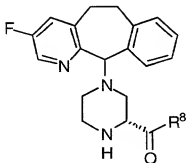


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TABLE 50

Ex.	C-11 isomer	R ⁸ =
355	S	
356	R	
357	S	
358	R	

PREPARATIVE EXAMPLE 162-165

- 5 By essentially the same procedure set forth in Preparative Example 115, only substituting the title compounds from the example listed in column 2 of Table 51, the title compounds of the formula shown below, with R⁸ as listed in column 4 of Table 51, can be prepared.

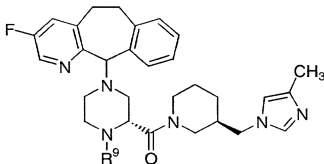


- 284 -
TABLE 51



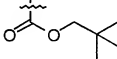
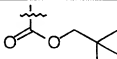
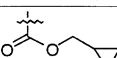
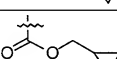




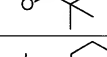
Prep Ex.	Ex.	C-11 isomer	R ⁸ =
162	355	S	
163	356	R	
164	357	S	
165	358	R	

EXAMPLES 359-370

- 5 By essentially the same procedure set forth in Example 14, only substituting the title compounds from the Preparative Example listed in column 2 of Table 52, the compounds of the formula shown below, with R⁹ as listed in column 4 of Table 52, can be obtained by using the appropriate electrophile.

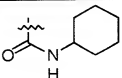


- 285 -
TABLE 52

Ex.	Prep. Ex.	C-11 isomer	R ⁹ =
359	163	R	
360	162	S	
361	163	R	
362	162	S	
363	163	R	
364	162	S	
365	163	R	
366	162	S	
367	163	R	
368	162	S	
369	163	R	

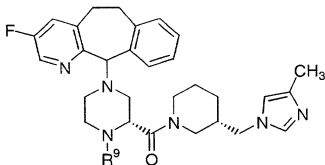
1002854-122001

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TABLE 52 - continued

Ex.	Prep. Ex.	C-11 isomer	R ⁹ =
370	162	S	



EXAMPLES 371-382

- 5 By essentially the same procedure set forth in Example 14, only substituting the title compounds from the Preparative Example listed in column 2 of Table 53, the compounds of the formula shown below, with R⁹ as listed in Column 4 of Table 53, can be obtained by using the appropriate electrophile.

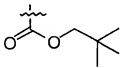
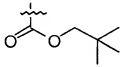
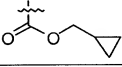
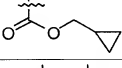




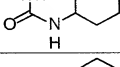
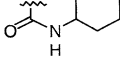


10

TABLE 53

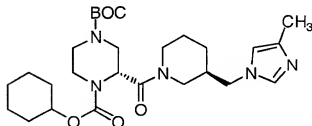
Ex.	Prep. Ex.	C-11 isomer	R ⁹ =
371	165	R	
372	164	S	

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TABLE 53 - continued

Ex.	Prep. Ex.	C-11 isomer	R ⁹ =
373	165	R	
374	164	S	
375	165	R	
376	164	S	
377	165	R	
378	164	S	
379	165	R	
380	164	S	
381	165	R	
382	164	S	

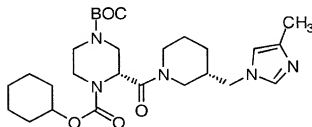
100221-15282001

PREPARATIVE EXAMPLE 166



- By essentially the same procedure set forth in Example 1 only substituting the title compound from Preparative Example 32 Step A and the title amine from Preparative Example 21, the title compound was prepared. FABMS: $MH^+ = 518$.

PREPARATIVE EXAMPLE 166A



- By essentially the same procedure set forth in Example 1 only substituting the title compound from Preparative Example 32 Step A and the title amine from Preparative Example 20, the title compound can be prepared.

PREPARATIVE EXAMPLES 167 and 168

- By essentially the same procedure set forth in Preparative Example 32, only substituting the title compounds from Preparative Example 166 and 166A and the 3-F, 8-H tricyclic chloride from Preparative Example 95, the compound of the formula shown below with R^8 as listed in Column 3 of Table 54 was prepared (Prep. Example 167) or can be prepared (Prep. Example 168).

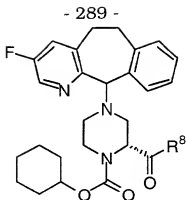


TABLE 54

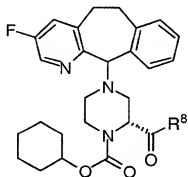
Prep. Ex.	C-11 isomer	R ⁸ =	CMPD
167	R,S		FABMS: MH ⁺ =629
168	R,S		---

5

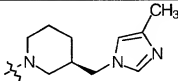
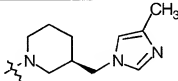
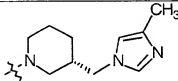
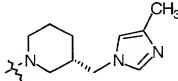
EXAMPLES 383-386

The title compounds from Preparative Examples 167 and 168 were (Preparative Examples 167) and can be (Preparative Example 168) separated into individual C-11 (S)- and (R)-diastereomers by

10 Preparative HPLC with a CHIRALPAK AD column using an iPrOH in hexanes solution with 0.2% DEA as eluent to give the compounds of the formula shown below with R⁸ as listed in Column 3 of Table 55.



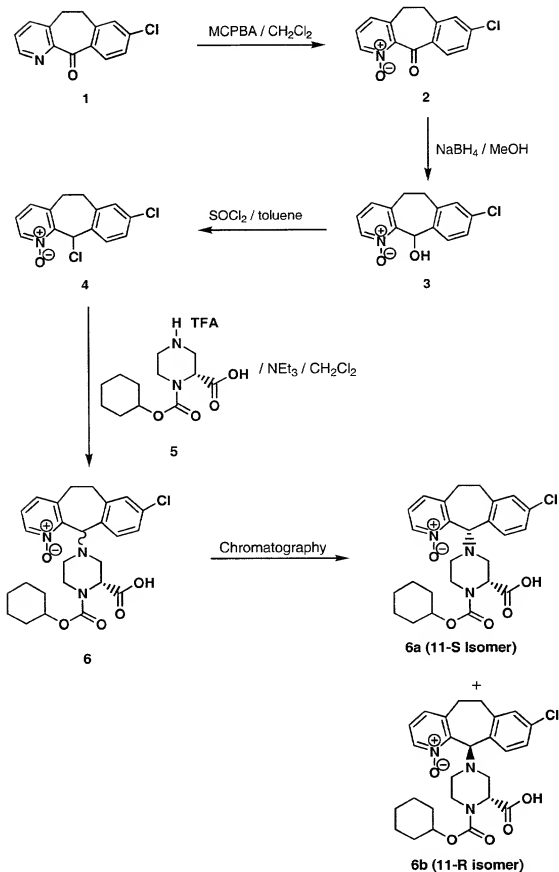
- 290 -
TABLE 55

Ex.	C-11 isomer	R ⁸ =	MP (°C)	CMPD
383	S		121-126	FABMS: MH ⁺ =629
384	R		104-111	FABMS: MH ⁺ =629
385	S		---	---
386	R		---	---

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PREPARATIVE EXAMPLE 168A

Preparation of the tricyclic N-oxide moiety



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1→**2** A solution of 3-peroxybenzoic acid (25 g, 102.59 mmol, 2.5 eq.) in anhydrous dichloromethane (250 mL) was added dropwise over a period of one hour to a stirred solution of 8-chloro-4-aza-10,11-dihydro-5*H*-dibenzo[a,d]cyclohepten-5-one **1** (10 g, 41.04 mmol, 1.0 eq.) in anhydrous dichloromethane (100 mL) at 0 °C under a nitrogen atmosphere. The solution was slowly (3h) warmed to room temperature and stirred for another 12h. The solution was extracted with 1 *M* aqueous sodium hydroxide solution (5 x 100 mL), washed with brine (2 x 100 mL), dried over Na₂SO₄, filtered, and concentrated under house vacuum at 30 °C to give **2** as a canary-yellow solid. The title compound **2** was used directly without further attempts at purification.

Yield: 10 g = 38.51 mmol = 94%

[M + H]⁺: 260

15 HRMS (FAB⁺):

Calculated for C₁₄H₁₁ClNO₂ ([M + H]⁺): 260.0475

Observed: 260.0478

2→**3** Sodium borohydride (2.21 g, 57.76 mmol, 1.5 eq.) was added portionwise over a period of 15 minutes to a solution of **2** (10 g, 38.51 mmol, 1.0 eq.) in anhydrous methanol (500 mL) at 0 °C under a nitrogen atmosphere. The resulting suspension was stirred at 0 °C for one hour and at room temperature for another hour. The volatiles were removed under house vacuum at 30 °C and the residue was taken up in 1 *M* aqueous NaOH solution (250 mL). The aqueous solution was extracted with dichloromethane (5 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried over Na₂SO₄, filtered, and concentrated under house vacuum at 30 °C to give **3** as a lime-green solid. Compound **3** was used directly without any attempts at purification.

Yield: 9 g = 34.39 mmol = 89%

[M + H]⁺: 262

HRMS (FAB⁺):

- 293 -
Calculated for $C_{14}H_{13}ClNO_2$ ($[M + H]^+$): 262.0635
Observed: 262.0636

- 3→4 Thionyl chloride (5 mL, 68.78 mmol, 2.0 eq.) was added
- 5 dropwise over a period of 10 minutes to a stirred suspension of **3** (9 g, 34.39 mmol, 1.0 eq.) and anhydrous toluene (150 mL) at 0 °C under a nitrogen atmosphere. The cream-colored suspension was slowly (3h) warmed to room temperature and stirred for another 12h. The volatiles were removed under house vacuum at 30 °C.
- 10 The residue was taken up in dichloromethane (250 mL) and washed with ice-cold, saturated aqueous $NaHCO_3$ solution (5 x 100 mL) until the aqueous washings were moderately basic at pH 9. The organic layer was washed with brine (100 mL), dried over Na_2SO_4 , filtered, and concentrated under house vacuum at 30 °C to give **4** as
- 15 a cream-colored solid in essentially quantitative yield. Due to its high reactivity, compound **4** was used directly without any attempts at purification or characterization (other than 1H NMR).

Yield: 9.55 g = 34.09 mmol = 99%

- 20 4→6 Triethylamine (18 mL, 126.65 mmol, 5.0 eq.) was added dropwise to a stirred solution of **5** (previously described in the art; 9.38 g, 25.33 mmol, 1.0 eq.) in anhydrous dichloromethane (50 mL) at room temperature under a nitrogen atmosphere. The solution was stirred at room temperature for 30 minutes and was cooled to 0
- 25 °C. A solution of **4** (8.52 g, 30.39 mmol, 1.2 eq.) in anhydrous dichloromethane (50 mL) was added dropwise over a period of 25 minutes. The mixture was slowly (3h) warmed to room temperature and stirred for another 12h. The volatiles were removed under house vacuum at 30 °C. The residue was taken up in 50% m/v
- 30 aqueous citric acid solution (100 mL) and extracted with ethyl acetate (5 x 100 mL). The organic extracts were combined and dried over Na_2SO_4 , filtered, and concentrated under house vacuum at 30 °C. The residual cream-colored solid was flash-chromatographed

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(CH₂Cl₂:MeOH = 19:1 v/v) to give the diastereomerically pure isomers **6a** and **6b** at C-11 of the tricycle.

For 6a:

Yield: 5.75 g = 11.50 mmol = 45%

5 Off-white foam; M.p.: 78-83 °C

[M + H]⁺: 500

HRMS (FAB+):

Calculated for C₂₆H₃₁ClN₃O₅ ([M + H]⁺): 500.1953

Observed: 500.1952

10 **For 6b:**

Yield: 3.00 g = 6.00 mmol = 24%

Off-white solid; M.p.: 94-99 °C

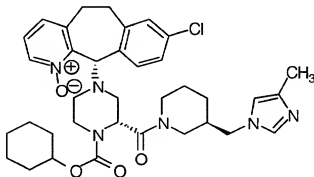
[M + H]⁺: 500

HRMS (FAB+):

15 Calculated for C₂₆H₃₁ClN₃O₅ ([M + H]⁺): 500.1953

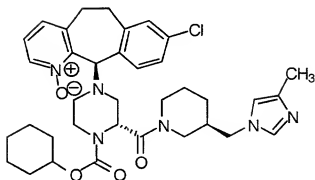
Observed: 500.1952

EXAMPLE 387



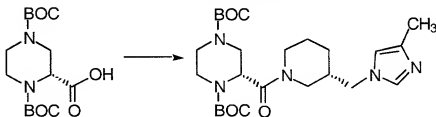
20 By essentially the same procedure set forth in Example 47A, only substituting the title compound from Preparative Example 168A, the title compound was prepared: mp = 85-90 °C; [M+H]⁺: 661.

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EXAMPLE 388



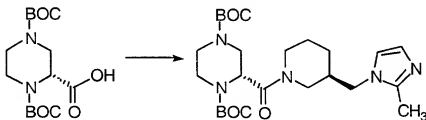
- By essentially the same procedure set forth in Example 42 (see Table 6), only substituting the title compound from Preparative
- 5 Example 168A, the title compound was prepared: mp = 108-113 °C; [M+H]⁺: 661.

PREPARATIVE EXAMPLE 169



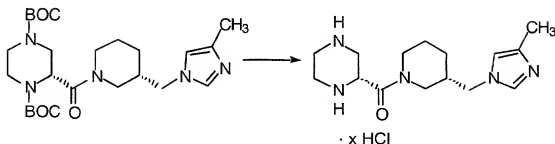
- 10 By essentially the same procedure set forth in Example 1, only substituting the title compound from Preparative Example 2 and substituting the appropriate amine, the title compound was prepared.

15 PREPARATIVE EXAMPLE 170



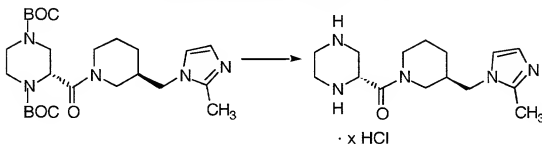
- By essentially the same procedure set forth in Preparative Example 147, the title compound was prepared.

PREPARATIVE EXAMPLE 171



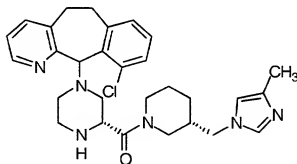
By essentially the same procedure set forth in Preparative Example 8, the title compound was prepared and used without further purification.

PREPARATIVE EXAMPLE 172



By essentially the same procedure set forth in Preparative Example 8, the title compound was prepared and used without further purification.

PREPARATIVE EXAMPLE 173



By essentially the same procedure set forth in Preparative Example 6, only substituting the title compounds from Preparative Example 171 and Preparative Example 99, the title compound was obtained: FABMS: $\text{MH}^+=519$.

- By essentially the same procedure set forth in Example 14, only substituting the title compounds from the Preparative Example listed in column 2 of Table 56, the compounds of the formula shown below, with R⁹ as listed in column 4 of Table 56, were obtained by
- 5 using the appropriate acylating agent.

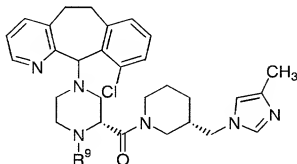



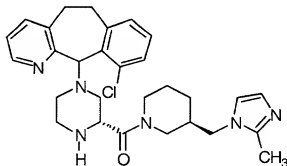
TABLE 56

Ex.	Prep. Ex.	C-11 isomer	R ⁹ =	CPMD
389	173	R		FABMS: MH ⁺ =644
390	173	S		FABMS: MH ⁺ =644
391	173	A		FABMS: MH ⁺ =645
230	173	B		FABMS: MH ⁺ =645
393	173	R		FABMS: MH ⁺ =619

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TABLE 56 - continued

Ex.	Prep. Ex.	C-11 isomer	R ⁹ =	CPD
394	173	S		FABMS: MH ⁺ =619

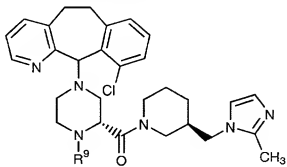
PREPARATIVE EXAMPLE 174



By essentially the same procedure set forth in Preparative Example 6, only substituting the title compounds from Preparative Example 172 and Preparative Example 99 the title compound was obtained: FABMS: MH⁺=519.

EXAMPLES 395-397

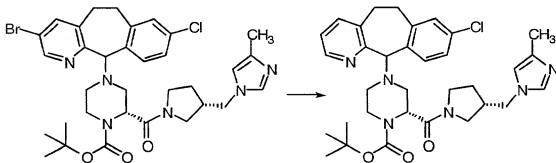
By essentially the same procedure set forth in Example 14, only substituting the title compounds from the Preparative Example listed in column 2 of Table 57, the compounds of the formula shown below, with R⁹ as listed in column 4 of Table 57, was obtained by using the appropriate acylating agent.



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TABLE 57

Ex.	Prep. Ex.	C-11 isomer	R=	CMPD
395	174	R,S		FABMS: MH ⁺ =619
396	174	A		FABMS: MH ⁺ =619
397	174	B		FABMS: MH ⁺ =619

EXAMPLE 398



The title compound from Example 165 (0.076 g) was balloon hydrogenated over 10% Pd/C (0.025 g) in EtOH (15 mL) overnight at room temperature. The catalyst and the solvent removed to give the title compound: MS MH⁺= 606.

EXAMPLES 399-402

By essentially the same procedures set forth in Preparative Example 24 and Example 14, only using the title compound from Example 398, the title compounds of the formula shown below, with R⁹ listed in column 3 of Table 58, were obtained.

- 300 -

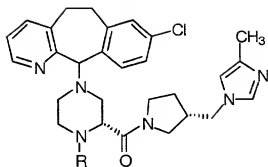


TABLE 58

Ex.	C-11 isomer	R ⁹ =	COMPD
399	S		FABMS: MH ⁺ =632
400	S		FABMS: MH ⁺ =592
401	S		FABMS: MH ⁺ =620
402	S		FABMS: MH ⁺ =605

5

EXAMPLES 403-406

By essentially the same procedure set forth in Example 399, compounds of the formula shown below, with R⁹ listed in column 4 of Table 59, were obtained.

10

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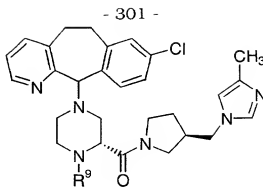


TABLE 59

Ex.	C-11 isomer	R ⁹ =	COMPD
403	S		FABMS: MH ⁺ =632
404	S		FABMS: MH ⁺ =592
405	S		FABMS: MH ⁺ =620
406	S		FABMS: MH ⁺ =605

5

EXAMPLES 407-408

By essentially the same procedure set forth in Example 1,
only substituting the appropriate amine, the compounds of the
formula shown below, with R⁸ as listed in column 3 of Table 60 were
obtained.

10

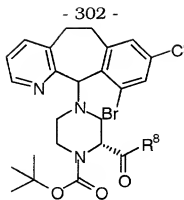


TABLE 60

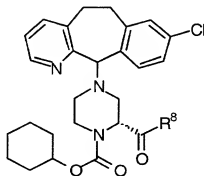
Ex.	C-11 isomer	R ⁸ =	CPD
407	1		FABMS: MH ⁺ =699
408	2		FABMS: MH ⁺ =699

5

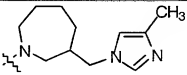
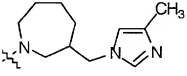
EXAMPLES 409 and 410

The title compound from Example 47(CC) was separated into individual diastereomers using a CHIRALPAK AD column using a 15% iPrOH in hexanes with 0.2% DEA as eluent to give the title compounds of formula shown below wherein R⁸ is as defined in column 3 of Table 60A.

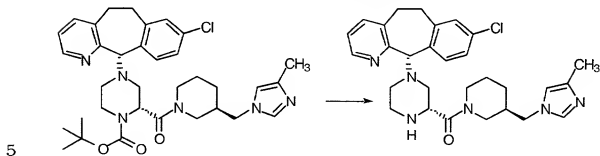
10



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TABLE 60A

Ex.	C-11 isomer	R ⁸ =	CPMPD
409	S	 Isomer 1	FABMS: MH ⁺ =659
410	S	 Isomer 2	FABMS: MH ⁺ =659

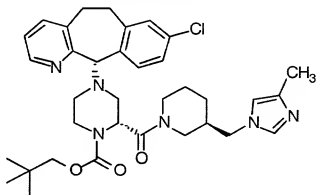
PREPARATIVE EXAMPLE 175



By essentially the same procedure put forth in Preparative Example 115 only substituting the title compound from Example 32, the title compound was prepared.

10

EXAMPLE 411



By essentially the same procedure set forth in Example 14, only substituting the title compound from Preparative Example 175 and neopentyl chloroformate, the title compound was prepared: mp=103-115 °C; LCMS: MH⁺=633.]

5

EXAMPLES 412 and 413

The title compounds of the formula shown below with R⁹ as listed in column 3 of the Table 61 were prepared by essentially the same procedure as set forth in Example 1, only substituting the title compound from Preparative Example 175 and the appropriate carboxylic acid.

10

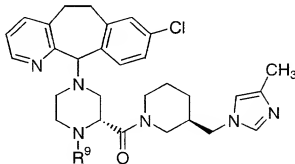
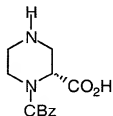


TABLE 61

Ex.	C-11 isomer	R ⁹ =	MP (°C)	CMPD
412	S		175 (dec.)	FABMS: MH ⁺ =654
413	S		150-152	FABMS: MH ⁺ =687

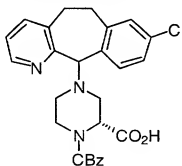
15

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PREPARATIVE EXAMPLE 175A



By essentially the same procedure set forth in Preparative
Example 31, Step A only substituting CBz-NOS for isopropyl
5 chloroformate, the title compound was prepared.

PREPARATIVE EXAMPLES 175B and 175C



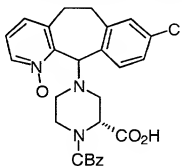
By essentially the same procedure set forth in Preparative
10 Example 31, Step B only substituting the title compound from
Preparative Example 175A, the title compounds (individual C-11
(S)- and (R)-isomers) were prepared.

Example 175B: C-11 (S)-isomer, Yield=13%, MH⁺=492.

Example 175C: C-11 (R)-isomer, Yield=13%, MH⁺=492.

15

PREPARATIVE EXAMPLES 175D and 175E

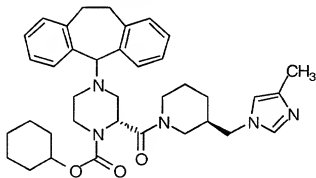


By essentially the same procedure set forth in Preparative Example 31, Step B only substituting the title compounds from Preparative Example 97 and Preparative Example 175A, the title compounds (individual C-11 (S)- and (R)-isomers) were prepared.

5 Example 175D: C-11 (S)-isomer, Yield=12%, $MH^+=508$.

Example 175E: C-11 (R)-isomer, Yield=15%, $MH^+=508$.

EXAMPLE 414

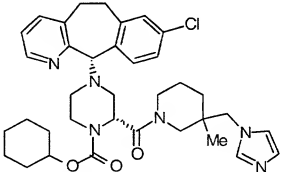
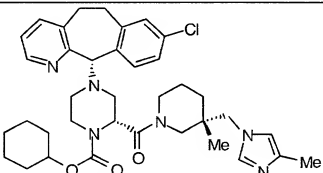
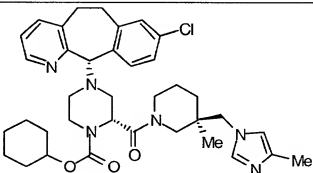


10 The title compound was prepared by essentially the same procedure as set forth in Example 387, only substituting the dibenzosuberonyl chloride for the tricyclic chloride: mp=98-112 °C; FABMS: $MH^+=610$.]

EXAMPLES 415-425

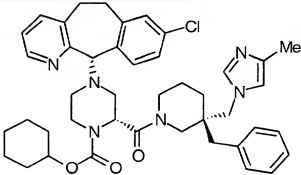
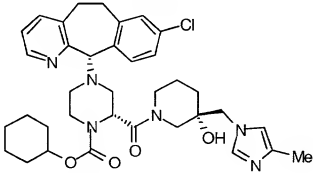
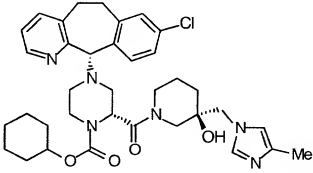
15 Following essentially the same procedure set forth in Example 1, only substituting the Carboxylic acid (11-(S) or 11-(R) isomer) from the Preparative Example listed in Table 62 and the appropriately substituted piperidine (Amine), the pure isomeric
20 products were prepared and separated by Preparative HPLC (AD column) using IPA-hexanes.

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TABLE 62

Ex.	Prep. Ex. 1. Amine 2. Acid	Product
415	1. 68 Step E 2. 32 11(S) isomer	 <p>1. Yield (%): 82 2. MH⁺: 645 3. mp (°C): 116.2</p>
416	1. 80 Step D 2. 32 11(S) isomer	 <p>1. Yield (%): 50.8 2. MH⁺: 659 3. mp (°C): 112.5-116.3</p>
417	1. 81 2. 32 11(S) isomer	 <p>1. Yield (%): 51.4 2. MH⁺: 659 3. mp (°C): 85.1-115</p>

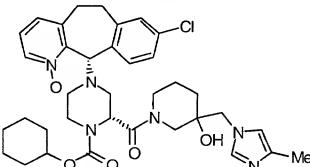
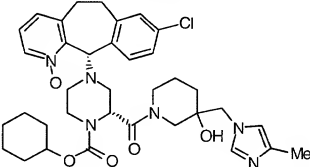
10028251-120001

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TABLE 62 - continued

Ex.	Prep. Ex. 1. Amine 2. Acid	Product
418	1. 82 Step B 2. 32 11(S) isomer	 <p>1. Yield (%): 63 2. MH⁺: 735 3. mp (°C): 135.9</p>
419	1. 83 Step E 2. 32 11(S) isomer	<p><u>Isomer A</u></p>  <p>1. Yield (%): 35.7 2. MH⁺: 661 3. mp (°C): 117.6-124.8</p> <p><u>Isomer B</u></p>  <p>1. Yield (%): 35.7 2. MH⁺: 661 3. mp (°C): 95.7-107.2</p>

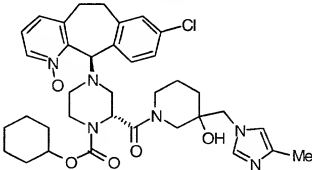
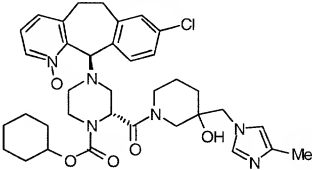
100221-122001

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TABLE 62 - continued

Ex.	Prep. Ex. 1. Amine 2. Acid	Product
420	1. 83 Step E 2. 168A 11(S) isomer	<p><u>Isomer A</u></p>  <p>1. Yield (%): 36 2. MH⁺: 677 3. mp (°C): 172.4</p> <p><u>Isomer B</u></p>  <p>1. Yield (%): 36 2. MH⁺: 677 3. mp (°C): 152.9</p>

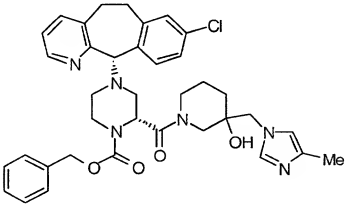
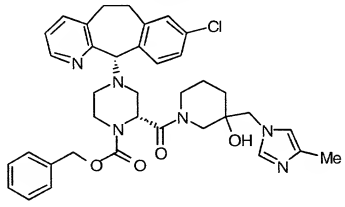
100221-15282001

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Table 62 - CONTINUED

Ex.	Prep. Ex. 1. Amine 2. Acid	Product
421	1. 83 Step E 2. 168A 11(R) isomer	<p><u>Isomer A</u></p>  <p>1. Yield (%): 50 2. MH⁺: 677 3. mp (°C): 152.6</p> <p><u>Isomer B</u></p>  <p>1. Yield (%): 50 2. MH⁺: 677 3. mp (°C): 145.4</p>

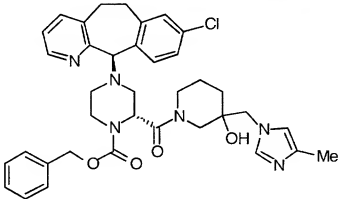
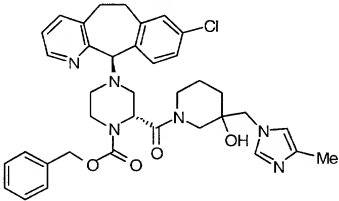
100221-15282001

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Table 62 - continued

Ex.	Prep. Ex. 1. Amine 2. Acid	Product
422	1. 83 Step E 2. 175B 11(S) isomer	<p><u>Isomer A</u></p>  <p>1. Yield (%): 32.7 2. MH⁺: 669 3. mp (°C): 142.2-150.9</p> <p><u>Isomer B</u></p>  <p>1. Yield (%): 32.7 2. MH⁺: 669 3. mp (°C): 133.2-148.1</p>

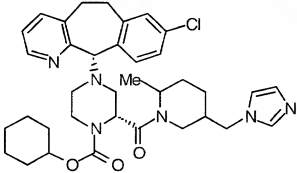
100221-15282001

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TABLE 62 - continued

Ex.	Prep. Ex. 1. Amine 2. Acid	Product
423	1. 83 Step E 2. 175C 11(R) isomer	<p><u>Isomer A</u></p>  <p>1. Yield (%): 27 2. MH⁺: 669 3. mp (°C): 117.7</p> <p><u>Isomer B</u></p>  <p>1. Yield (%): 32 2. MH⁺: 669 3. mp (°C): 140.1</p>

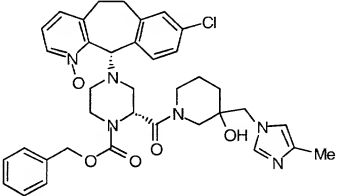
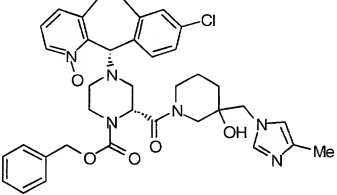
10028251-122001

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TABLE 62 - continued

Ex.	Prep. Ex. 1. Amine 2. Acid	Product
424	1. 66 Step G 2. 32 11(S) isomer	 <p> 1. Yield (%): 54.5 2. MH⁺: 645 3. mp (°C): 127.3 </p>

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TABLE 62 - continued

Ex.	Prep. Ex. 1. Amine 2. Acid	Product
425	1. 83 Step E 2. 175D 11(S) isomer	<p data-bbox="578 286 664 306"><u>Isomer A</u></p>  <p data-bbox="401 580 596 655"> 1. Yield (%): 35 2. MH⁺: 685 3. mp (°C): 140-142 </p> <p data-bbox="578 665 664 685"><u>Isomer B</u></p>  <p data-bbox="401 933 596 1008"> 1. Yield (%): 19 2. MH⁺: 685 3. mp (°C): 133-135 </p>

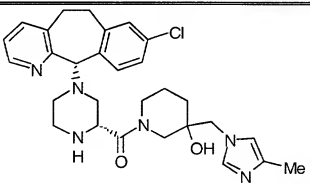
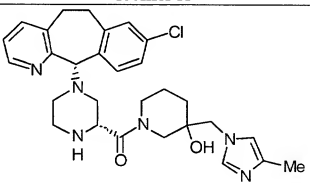
10026251-122001

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PREPARATIVE EXAMPLES 176-179

Stirring the benzyloxycarbonyl (CBZ) compounds listed in
 Column 2 of Table 63 and Palladium on carbon catalyst in EtOH
 under 1 atmosphere of hydrogen gas afforded the Product amines.

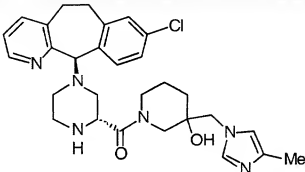
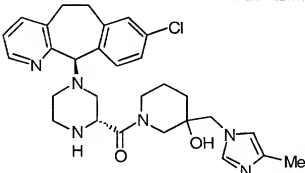
5

TABLE 63

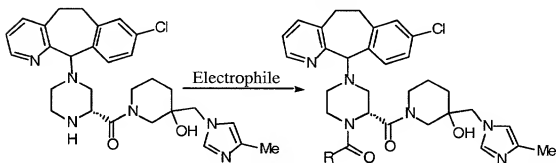
Prep. Ex.	CBZ compound from Example No.	Product
176	422 Isomer A	 <p>1. Yield (%): 95 2. MH⁺: 535</p> <p style="text-align: center;">Isomer A</p>
177	422 Isomer B	 <p>1. Yield (%): 82 2. MH⁺: 535</p> <p style="text-align: center;">Isomer B</p>

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TABLE 63 - continued

Prep. Ex.	CBZ compound from Example No.	Product
178	423 Isomer A	 <p>Isomer A</p>
179	423 Isomer B	 <p>Isomer B</p>

EXAMPLES 426-434




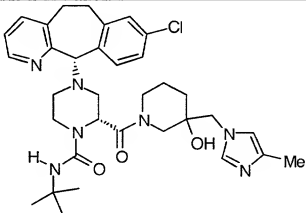

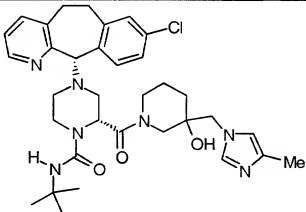
5

By essentially the same procedure as set forth in Example 14, only substituting the piperazine amines (isomer A or B) listed in column 2 of Table 64 for the title compound from Preparative

Example 24, and using as the Electrophile either an isocyanate to give the urea products, or a carboxylic acid, HOBT, DEC and DMF to give the amide products listed in Table 64.


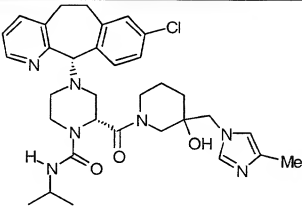

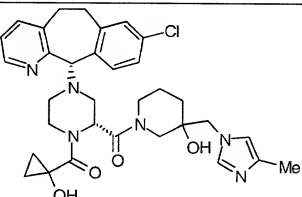
5

TABLE 64


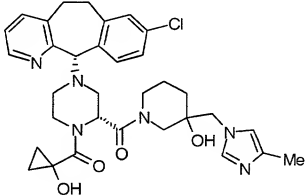

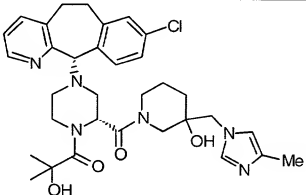
Ex.	Prep. Ex. No. of Amine Electrophile	Product
426	1. 176 2. 	 <p>1. Yield (%): 100 2. MH⁺: 634 3. mp (°C): 240.2-253.7 Isomer A</p>
427	1. 177 2. 	 <p>1. Yield (%): 100 2. MH⁺: 634 3. mp (°C): 148.7-164.2 Isomer B</p>

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TABLE 64 - continued


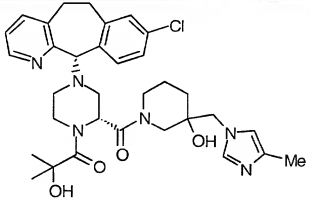

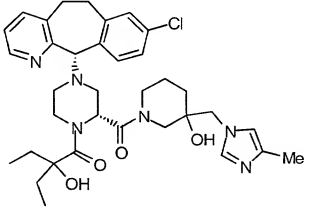
Ex.	Prep. Ex. No. of Amine Electrophile	Product
428	1. 176 2. 	 <p>1. Yield (%): 75 2. MH⁺: 620 3. mp (°C): 165.5-178.2 Isomer A</p>
429	1. 176 2. 	 <p>1. Yield (%): 21.4 2. MH⁺: 619 3. mp (°C): 148.7-168.3 Isomer A</p>

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TABLE 64 - continued

Ex.	Prep. Ex. No. of Amine Electrophile	Product
430	1. 177 2. 	 <p>1. Yield (%): 10 2. MH⁺: 619 3. mp (°C): 169.2-190.9 Isomer B</p>
431	1. 176 2. 	 <p>1. Yield (%): 29 2. MH⁺: 621 3. mp (°C): 146.5-153.6 Isomer A</p>


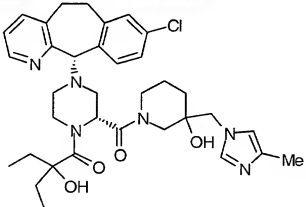

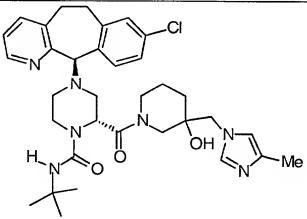
100221 15282001

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TABLE 64 - continued

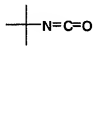
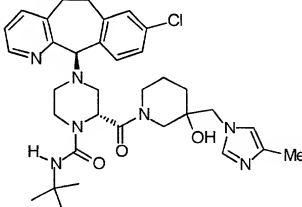
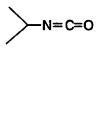
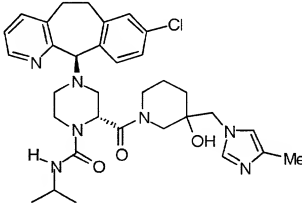
Ex.	Prep. Ex. No. of Amine Electrophile	Product
432	1. 177 2. 	 <p>1. Yield (%): 31 2. MH⁺: 621 3. mp (°C): 138.3-161.3 Isomer B</p>
433	1. 176 2. 	 <p>1. Yield (%): 36 2. MH⁺: 649 3. mp (°C): 123.4-133.9 Isomer A</p>

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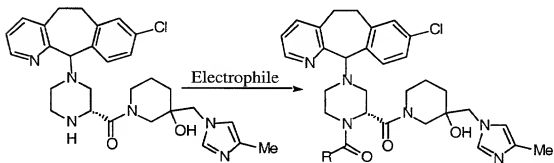
- 321 -
TABLE 64 - continued

Ex.	Prep. Ex. No. of Amine Electrophile	Product
434	1. 177 2. 	 1. Yield (%): 35 2. MH ⁺ : 649 3. mp (°C): 119.3-135.7 Isomer B
435	1. 178 2. 	 1. Yield (%): 63 2. MH ⁺ : 634 3. mp (°C): 159.2 Isomer A

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
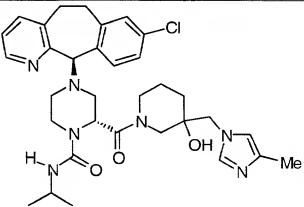

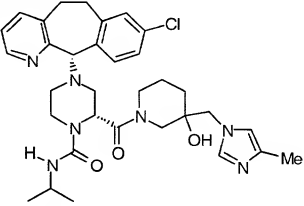
<p>436</p>	<p>1. 179</p> <p>2.</p> 	 <p>1. Yield (%): 69 2. MH⁺: 634 3. mp (°C): 175</p> <p>Isomer B</p>
<p>437</p>	<p>1. 178</p> <p>2.</p> 	 <p>1. Yield (%): 77 2. MH⁺: 620 3. mp (°C): 167.2</p> <p>Isomer A</p>

EXAMPLES 438-457




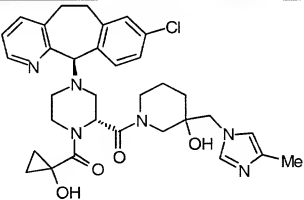

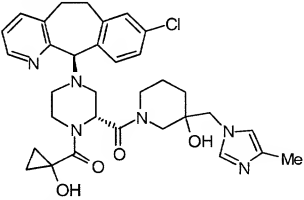

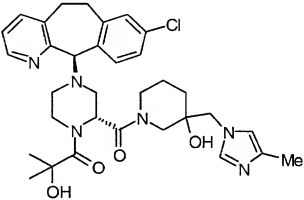
If the procedure described for Example 426 were followed using the piperazine amines (isomer A or B) listed in column 2 of Table 65 and, as the Electrophile, either an isocyanate, or a carboxylic acid and HOBt, DEC and DMF, then the urea or amide products, respectively, listed in Table 65 would be obtained.

TABLE 65

Ex.	Prep. Ex. No. of Amine Electrophile	Product
438	1. 179 2. 	 Isomer B
439	1. 177 2. 	 Isomer B


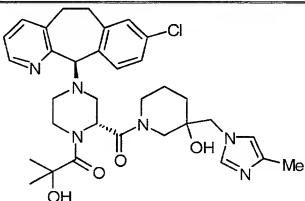

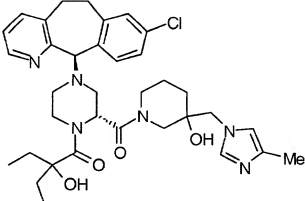

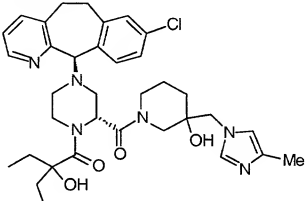
10028251-122001

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TABLE 65 - CONTINUED

Ex.	Prep. Ex. No. of Amine Electrophile	Product
440	1. 178 2. 	 Isomer A
441	1. 179 2. 	 Isomer B
442	1. 178 2. 	 Isomer A

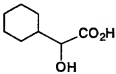
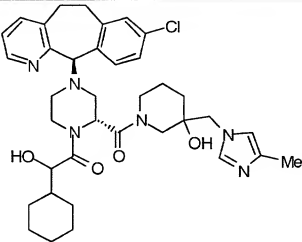
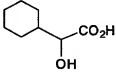
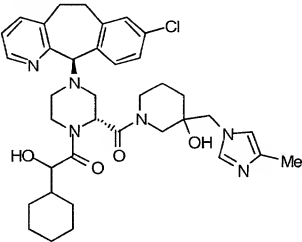
1002851-122001

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Table 65 - CONTINUED

Ex.	Prep. Ex. No. of Amine Electrophile	Product
443	1. 179 2. 	 Isomer B
444	1. 178 2. 	 Isomer A
445	1. 179 2. 	 Isomer B

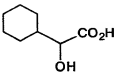
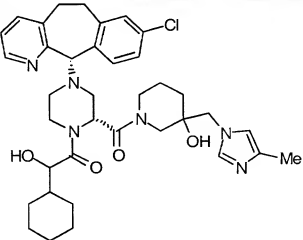
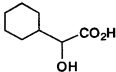
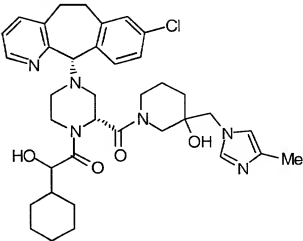

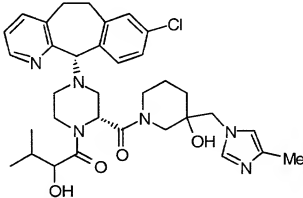
100221-1528201

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Table 65 - continued

Ex.	Prep. Ex. No. of Amine Electrophile	Product
446	1. 178 2. 	 Isomer A
447	1. 179 2. 	 Isomer B


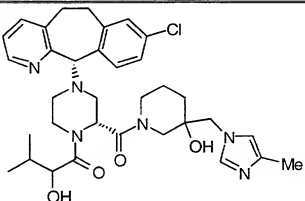

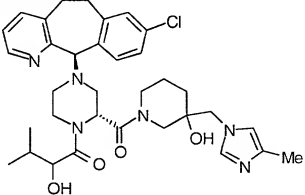

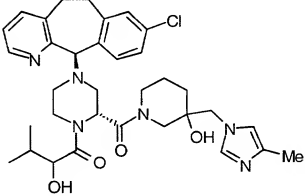
10028251-122001

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TABLE 65 - continued

Ex.	Prep. Ex. No. of Amine Electrophile	Product
448	1. 176 2. 	 Isomer A
449	1. 177 2. 	 Isomer B
450	1. 176 2. 	 Isomer A

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TABLE 65 - continued

Ex.	Prep. Ex. No. of Amine Electrophile	Product
451	1. 177 2. 	 Isomer B
452	1. 178 2. 	 Isomer A
453	1. 179 2. 	 Isomer B

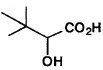
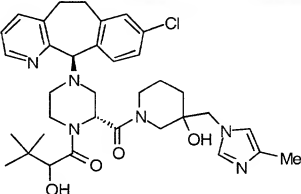
100221-15282001

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TABLE 65 - continued

Ex.	Prep. Ex. No. of Amine Electrophile	Product
454	1. 176 2.	 Isomer A
455	1. 177 2.	 Isomer B
456	1. 178 2.	 Isomer A

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
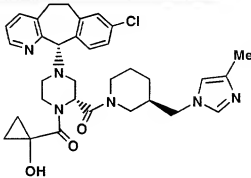

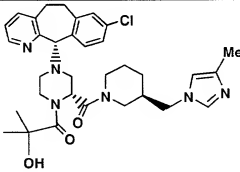

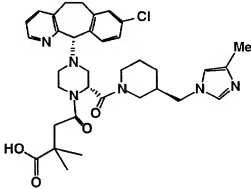
- 330 -
TABLE 65 - continued

Ex.	Prep. Ex. No. of Amine Electrophile	Product
457	1. 179 2. 	 Isomer B

EXAMPLES 458-463


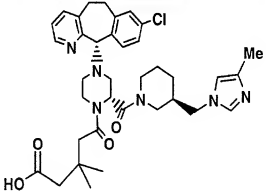
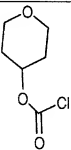
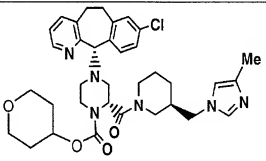
- 5 Using a similar procedure as that described for Example 14,
only using the piperazine amine from Preparative Example 175
instead of the title compound from Preparative Example 24, and
using as the Electrophile either a chloroformate to give a carbamate
or an anhydride, or a carboxylic acid, HOBt, DEC and DMF to give
10 the amide products listed in Table 66.

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Table 66

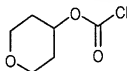
Ex.	Electrophile	Product	1. Yield (%) 2. MH ⁺ 3. mp (°C)
458			1. 54.1 2. 603 3. 145.2
459			1. 67.8 2. 605 3. 86.7
462			1. 100 2. 647 3. 86.2

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TABLE 66 - continued

Ex.	Electrophile	Product	1. Yield (%) 2. MH ⁺ 3. mp (°C)
463			1. 100 2. 661 3. 65.1
463A			1. 85 2. 647 3. 52.1

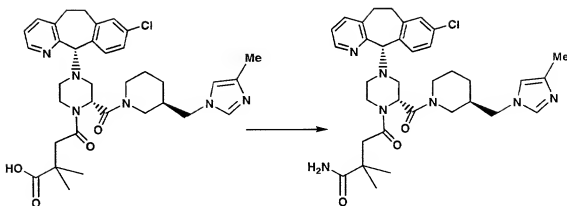
PREPARATIVE EXAMPLE 180



5

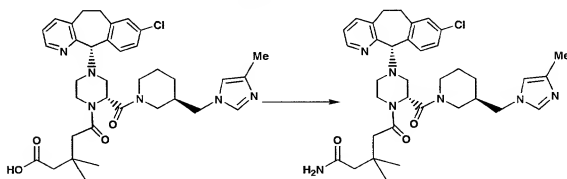
Following essentially the same procedure as that used in Example 466 Step A, except using tetrahydro-4H-pyran-4-ol, the title compound was prepared (3.1g, 78%, MH⁺=165).

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EXAMPLE 464



The title compound from Preparative Example 462 (0.205 g), 0.5M ammonia in dioxane (2 mL), DEC (0.175 g), HOBt (0.123 g) and anhydrous DMF (5 mL) were stirred at room temperature overnight. Purification by preparative plate chromatography (silica, 5% MeOH-CH₂Cl₂, NH₄OH saturated) afforded the title compound (0.136 g, 66%, MH⁺ = 646).

EXAMPLE 465



The title compound from Preparative Example 463 (0.228 g), 0.5M ammonia in dioxane (2 mL), DEC (0.175 g), HOBt (0.123 g) and anhydrous DMF (5 mL) were stirred at room temperature overnight. Purification by preparative plate chromatography (silica, 5% MeOH-CH₂Cl₂, NH₄OH saturated) afforded the title compound (0.139 g, 61%, MH⁺ = 660).



10

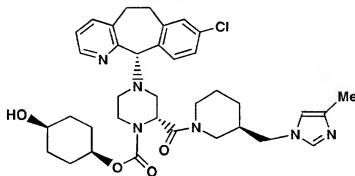
Chemical reaction scheme showing the synthesis of a substituted piperidine derivative. The reaction involves the esterification of a piperidine-2,6-dicarboxylic acid derivative with a complex amine. The starting material is a piperidine ring with a methyl ester group at position 2 and a carboxylic acid group at position 6, labeled "cis". The amine is a complex molecule featuring a 4-chloro-1,2,3,4-tetrahydroquinoline system, a piperidine ring, and a 4-methyl-1H-imidazole ring. The reaction is catalyzed by DMAP and DCC in CH₂Cl₂ at 0°C to room temperature for 24 hours. The product is a complex molecule where the piperidine ring from the starting material is linked to the complex amine via an ester bond, maintaining the "cis" configuration.

Combining the chloroformate (0.052 g) from Step A with the piperazine amine (0.103 g) from Preparative Example 175 and

following a similar procedure as that described in Example 14, the title compound was obtained (0.07 g, 50%, $MH^+ = 703$).

5

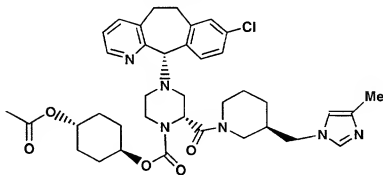
EXAMPLE 467



Treatment of the product from Example 466 (0.06 g) with potassium carbonate (0.2 g) in MeOH (2 mL) afforded the title compound (0.056 g, 100%, $MH^+ = 661$).

10

EXAMPLE 468



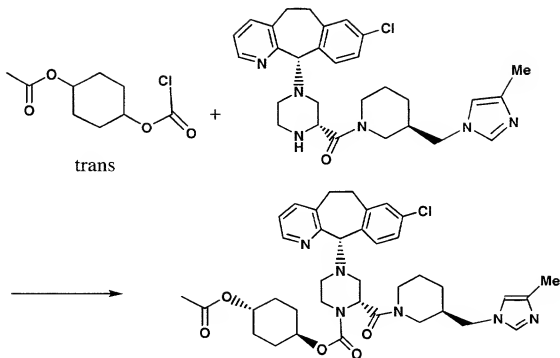
Step A

15



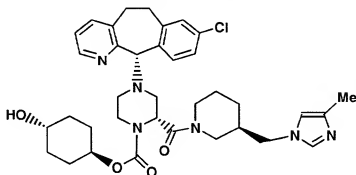
The commercially available *trans*-acetoxy-cyclohexanol (0.05 g) was treated with phosgene (0.5 mL). Concentration in vacuo afforded the chloroformate (0.062 g, 89%).

Step B



- Combining the chloroformate (0.062g) from Step A with the
 5 piperazine amine (0.103 g) from Preparative Example 175 and
 following a similar procedure as that described in Example 14, the
 title compound was obtained (0.058 g, 42%, $MH^+ = 703$).

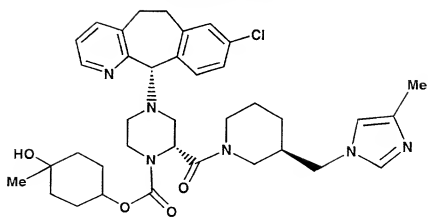
EXAMPLE 469



10

Treatment of the product from Example 466 (0.05 g) with
 potassium carbonate (0.2 g) in MeOH (2 mL) afforded the title
 compound (0.047 g, 100%, $MH^+ = 661$).

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EXAMPLE 470



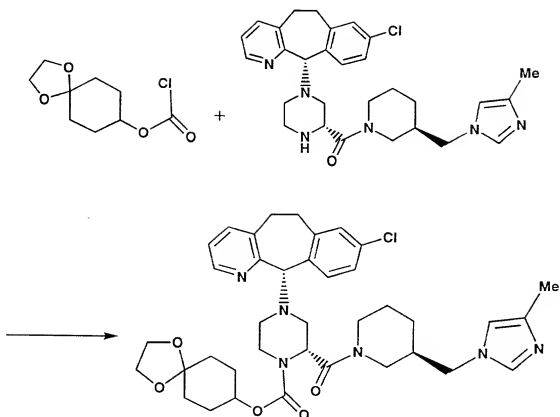
Step A

5



If the commercially available cyclohexanol were treated with phosgene then the chloroformate would be obtained.

Step B

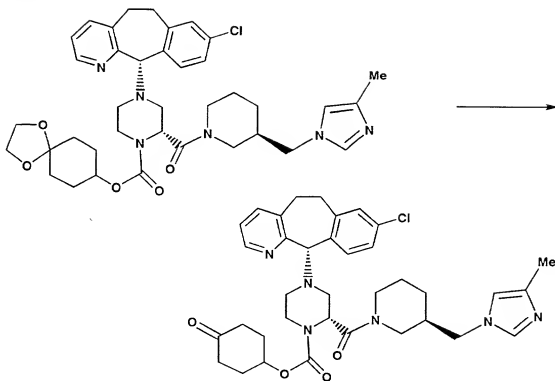


If the chloroformate from Step A were combined with the piperazine amine shown above according to the procedure described

5

for Example 461 then the ketal would be obtained.

Step C

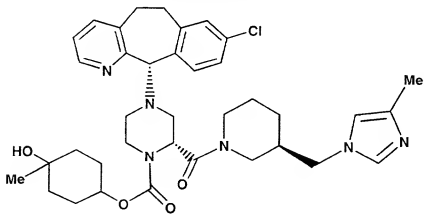


If the product of Step B were treated with aqueous acid the ketone would be obtained.

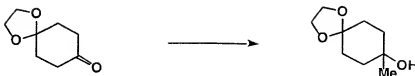
Step D

If the product of Step C were treated with MeMgBr or MeLi then the title product would be obtained.

EXAMPLE 471



Step A



If the commercially available ketone were treated with methyl magnesium bromide, then the desired alcohol would be obtained.

5

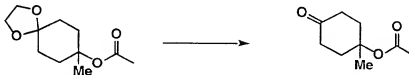
Step B



If the product of Step A above were treated with acetic anhydride, then the desired acetate would be obtained.

10

Step C



If the product of Step B were treated with formic acid, then the desired ketone would be obtained.

15

ASSAYS

FPT IC₅₀ (inhibition of farnesyl protein transferase, in vitro enzyme assay) was determined following the assay procedures described in WO 95/10516, published April 20, 1995. GGPT IC₅₀ (inhibition of geranylgeranyl protein transferase, in vitro enzyme assay), Cell Mat Assay, COS Cell IC₅₀ (Cell-Based Assay), and anti-tumor activity (in vivo anti-tumor studies) could be determined by the assay procedures described in WO 95/10516. The disclosure of WO 95/10516 is incorporated herein by reference thereto.

20

Additional assays can be carried out by following essentially the same procedure as described above, but with substitution of alternative indicator tumor cell lines in place of the T24-BAG cells.

25

The assays can be conducted using either DLD-1-BAG human colon carcinoma cells expressing an activated K-ras gene or SW620-BAG human colon carcinoma cells expressing an activated K-ras gene.

- Using other tumor cell lines known in the art, the activity of the compounds of this invention against other types of cancer cells could be demonstrated.

Soft Agar Assay:

- Anchorage-independent growth is a characteristic of tumorigenic cell lines. Human tumor cells can be suspended in growth medium containing 0.3% agarose and an indicated concentration of a farnesyl transferase inhibitor. The solution can be overlayed onto growth medium solidified with 0.6% agarose containing the same concentration of farnesyl transferase inhibitor as the top layer. After the top layer is solidified, plates can be incubated for 10-16 days at 37°C under 5% CO₂ to allow colony outgrowth. After incubation, the colonies can be stained by overlaying the agar with a solution of MTT (3-[4,5-dimethyl-thiazol-2-yl]-2,5-diphenyltetrazolium bromide, Thiazolyl blue) (1 mg/mL in PBS). Colonies can be counted and the IC₅₀'s can be determined.

- Compounds of this invention had an FPT IC₅₀ within the range of <0.04nM to 20nM, and a Soft Agar IC₅₀ within the range of <0.5nM to >500nM.

- Compounds of Examples 1-4, 4.1, 4.2, 5, 7, 8, 10-19, 24-51, and 74, 138, 142, 144, 145 had an FPT IC₅₀ within the range of <0.04nM to 2.7nM. Compounds of Examples 1-4, 4.1, 4.2, 5, 7, 10-19, 24-51, and 74, 138, 142, 144, 145 had a Soft Agar IC₅₀ within the range of <0.5nM to 30nM.

- Compounds of Examples 35(A), 35(C), 35(D), 35(E), 35(F), 41(A), 41(B), 41(C), 47(A), 47(B), 47(D), 47(G), 47(H), 47(I), 47(K), 47(L), 47(M), 47(N), 47(O), 47(P), 47(R), 47(S), 47(T), 47(U), 47(CC), 51(A) to 51 (D), 138 A to 147A, 148 to 158, 160, 161, 163, 169 to 180, 183 to 188, 191, 192, 197, 201, 207 to 216, 227 to 234, 238 to 240, 245, 255 to 262, 287 to 294, 297 to 303, 316 to 324, 351 to

354, 383, 384, 387, 388, 391, 392, 394 to 397, 407, 408, 409, 410, 411, 412, 414, 415 to 417, 419, 422 and 424 had an FPT IC₅₀ within the range of <0.04 to 2.7 nM, and a Soft Agar IC₅₀ within the range of <0.05 to 30 nM.

5 For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may
10 be comprised of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically
15 acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), Remington's Pharmaceutical Sciences, 18th Edition, (1990), Mack Publishing Co., Easton, Pennsylvania.

Liquid form preparations include solutions, suspensions and
20 emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

25 Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g. nitrogen.

Also included are solid form preparations which are intended
30 to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are

5 conventional in the art for this purpose.

Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired

10 purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 0.01 mg to about 1000 mg, preferably from about 0.01 mg to about 750 mg, more preferably from about 0.01 mg to about 500mg, and most preferably from

15 about 0.01 mg to about 250mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a

20 particular situation is within the skill of the art. For convenience, the total daily dosage may be divided and administered in portions during the day as required.

The amount and frequency of administration of the compounds of the invention and/or the pharmaceutically

25 acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 0.04 mg/day to about 4000

30 mg/day, in two to four divided doses.

While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to

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those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

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